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Sir Archibald Garrod's "Inborn Errors of Metabolism"

IV. Pentosuria

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"In many cases neurasthenic symptoms and neuralgic pains have been prominent. Others have been perfectly well when once freed from the restrictions of a diabetic regimen. Concerning the real nature of the malady, we can only say that it is an anomaly in the intermediary metabolism, rather analogous to cystinuria and alkaptonuria than to diabetes." *Essential Pentosuria in Two Brothers*, T. C. Janeway, 1906.

INTRODUCTION

UNTIL JANEWAY (1906) DESCRIBED the nineteenth and the first American case of pentosuria, the recognition of this disease had been almost limited to a few German clinics. Janeway's critical and scholarly article, from which comes the above quotation, indicates his familiarity with Garrod's (1902) précis of his concept of the inborn errors, though the latter did not mention pentosuria. Perhaps the quoted lines suggested to Garrod the inclusion of pentosuria with albinism, alkaptonuria and cystinuria as the inborn errors of metabilism. Garrod's contribution to the study of the disease was otherwise slight, since he had never seen a case, and at the time he wrote, the basic facts were hopelessly confused. He called it then, and later (Garrod, 1923), "the least known member of the group." The same kind of delay in comprehension and the same perpetuation of uncertainties in the medical literature that characterized the histories of the other inborn errors of metabolism (Knox, 1958) has plagued the study of pentosuria. It is still today less certainly known than the record shows when critically evaluated. It is still not known whether the neurasthenic symptoms are part of the disease or, as Janeway so nicely implied, the result from the threat of diabetes. Many texts leave the impression that pentosuria may not even be a disease entity, but a condition with many causes.

Well over 200 cases of chronic or essential pentosuria (also called xyloketosuria and xylulosuria) have now been described. There were 163 of these known by 1943 (Derivaux). Except for the first thirty or so cases known in Garrod's time that were imperfectly studied, and except for some minor and usually temporary excretions of various pentoses in certain situations, almost all of the known instances of pentosuria conform to the characteristic pattern of a single disease entity. This consists of the constant urinary excretion from infancy throughout life, almost independent of

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changes in diet, of about 2.0 to 3.5 g. per day of the reducing sugar, *L*-xylulose. There are no notable metabolic or clinical abnormalities, and the affected individuals have a normal life expectancy. The condition is inherited through a single autosomal recessive gene. It is almost entirely limited to Jews, but a few patients of non-Jewish Mediterranian or European origin have been described. There is a singular lack of reviews which discuss these several facets of the pentosuria problem, but articles by Janeway (1906), Greenwald (1922, chemical), Margolis (1929, clinical), Lasker, Enklewitz & Lasker (1936, genetics), and Lasker (1950, chemical) are authoritative considerations of their special fields.

ORIGIN OF THE CONFUSION ABOUT THE NATURE OF PENTOSURIA

The Identification of the Pentose: Like cystine and homogentisic acid, pentose was first found in the urine of patients with hereditary diseases. Blumenthal (1895) found a reducing substance in the urine of a patient in 1880, but this was not identified as a pentose until such substances had been recognized from plant sources and soon thereafter in the urine of the pentosuric described by Salkowski and Jastrowitz (1892). Then the pentose was recognized in the original case. But again like cystine and homogentisic acid, it now seems probable that the nature of the pentose was at first erroneously determined. Neuberg (1900), whose bizarre results in the study of cystinuria have already been described (Knox, 1958), isolated racemic arabinose from the urine of one of Salkowski's cases. "The most remarkable fact of all in regard to pentosuria is the optical inactivity of the excreted sugar (Garrod, 1909)". Such a substance almost always occurs in biological systems in one or the other of its optically active forms. The structures of the sugars in question are shown in Figure 1. All of them reduced Benedict's solution, the routine test which led to their discovery. The pentose was recognized and distinguished from glucose when it could not be fermented by yeast and by the formation of a relatively soluble, low melting osazone, but methods for distinguishing between the very similar pentoses were in their infancy. The optical rotation of xylulose is so low that, with the low concentrations of the pentose in the urine, the lack of optical activity in the urine led to the assumption that an inactive sugar was present. This initial uncertainty about the structure of the pentose was subsequently confounded by inconsistencies in the description of the enantiomorphs by the old prefixes *d*- and *l*-, referring to the optical rotation, and the modern prefix of *D*- or *L*-, which ignores the rotation and indicates the structural

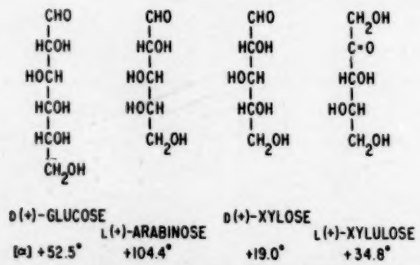

FIG. 1. Structures, *D*- or *L*- designations, and specific optical rotations [α] of some sugars related to the *L*-xylulose (xyloketose) excreted in pentosuria.

relationship of the compound to *D*- or *L*-glyceraldehyde. Zerner and Waltuch (1913) first developed a method based on a marked elevation of the melting point of the osazone when both optical forms were present, which indicated that the urinary sugar was optically active and was not arabinose. They sought to mitigate Neuberg's attack on their work by conceding that there might be two kinds of pentosuria, but the three patients they could check excreted a sugar like the one they had identified. The urinary sugar was promptly thereafter identified as xyloketose (xylulose) by Levene and LaForge (1914). This identification was confirmed in four patients (Greenwald, 1930). After incorrect designation of the optical form in the latter two papers was corrected (Greenwald, 1933), it was clear that the pentose found in the urine of most patients was *L*(+)-xylulose. Lasker (1950) admits on "seemingly good evidence" five reports of the excretion of racemic arabinosuria. The last was in 1928, but one of these cases examined by modern methods forty years later excreted xylulose (Barnes & Bloomberg, 1953). After a simple clinical method for identifying xylulose was developed, depending upon the reduction of Benedict's solution at 55° (Lasker & Enklewitz, 1933), the urinary pentose of another patient who 28 years earlier was thought to excrete arabinose was shown to excrete xylulose (Cohen & Gershenfeld, 1936).

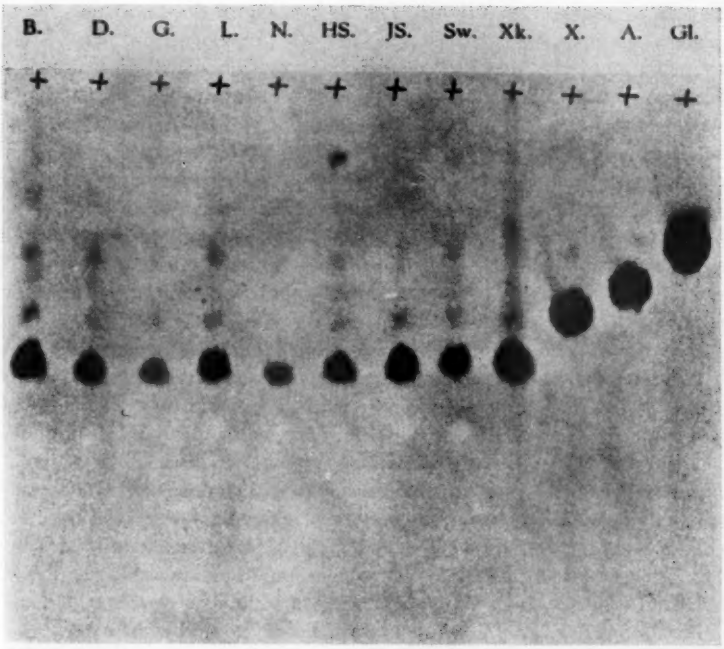

FIG. 2. Photograph of the chromatogram of reducing substances in eight specimens of pentosuric urines and four reference sugars applied at the marks (+). Xk = xyloketose (xylulose), X = xylose, A = arabinose, Gl = glucose. The base line represents the solvent front. (From Barnes and Bloomberg, 1953)

The surety and simplicity with which urinary pentoses can be identified by modern methods is illustrated by the reproduction in Figure 2 of Barnes' and Bloomberg's chromatograph of the urines of their eight patients. B is the patient believed to excrete racemic arabinose on the basis of early chemical studies (Aron, 1913). This method, and column chromatography which has permitted the demonstration that a pentosuric subject also excretes several hundred mg. of *L*-arabitol (Touster & Harwell, 1958), can eliminate any further uncertainty about the chemical anomaly in pentosuria.

PENTOSURIAS OTHER THAN XYLULOSURIA

DL-Arabinosuria: The existence of *DL*-arabinosuria is questionable. No case has been reported since 1928 and of those reported earlier only seven were supported by significant chemical evidence. All were obtained by this same method. One of these has been shown by modern methods to excrete xylulose. It is tempting to attribute these results to inadequate methods, but the derivatives and two separated forms isolated by Cammidge and Howard (1920) from the urines of three of their seven patients cannot be easily ignored. Numerous efforts to prepare similar compounds from known xylulose-containing urines have been unsuccessful. Not one case of arabinosuria has been found among 73 cases of pentosuria studied by Lasker (1950). If arabinosuria exists at all, it is extraordinarily rare and the fact that it does exist must be proved by modern methods.

Intermittent and Drug-Induced Pentosurias: Margolis reviewed nine cases in whom pentosuria appeared to be acquired. The possibility that low levels of pentose excretion would have been missed in previous urine examinations is very real. The first case of chronic pentosuria occurred in a morphine addict, as did the second. In the first case when the morphine was stopped, the pentosuria remained, but in the second case the pentosuria disappeared when the morphine intake was discontinued. With the exception of the pronounced xylulosuria caused by amidopyrine administration (Margolis, 1929), it is probable that the pentosurias reported in patients taking drugs represent drug-conjugated glycuronates which appear in the urine and give the pentose reaction.

Pentosuria in Diabetes: The high frequency of pentose excretion by diabetics which was formerly recorded has not been substantiated. It is also established that pentosurics rarely have abnormal glucose metabolism. Pentosurics frequently give a family history of diabetes, but both conditions are common in Jews. If both diabetes and pentosuria appear in the same individual, they do so as distinct metabolic entities.

Alimentary Pentosuria: It is an undoubted fact that pentose excretion occurs when a normal man is fed some pentose in an amount above the normal tolerance for that particular sugar. Such studies have usually been performed with *L*-arabinose or *D*-xylose. The same result can follow over-ingestion of certain fruits rich in pentose. Seventeen of 18 individuals who drank 1.5 liters of apple juice developed a temporary pentosuria (Johnstone, 1906). Xylose and arabinose are said to be excreted in such alimentary pentosuria from natural foods, but no convincing chemical evidence of the structure of the excreted sugar appears to be available. Alimentary pentosuria is also much more readily produced in some individuals than in others. The coexistence

of renal glycosuria with alimentary pentosuria produced by a diet which did not cause pentosuria in other individuals was reported by Dunsky and Lawrence (1947). Since xylose is reabsorbed in the kidney tubule by the same transport system that acts on glucose (Shannon, 1948), it should not be surprising that the renal glycosurics who lack this system would also readily excrete the pentose.

The excretion of trace amounts of pentoses, amounts several orders of magnitude smaller than those concerned in pentosuria have recently been described in normal man (Futterman and Roe, 1955), in neuromuscular disease (Tower, Peters, and Pogowelskin, 1956), and in cold-stressed or thyroid treated rats (Roe and Coover, 1950). There is no possibility of confusion between these variations in the very small normal output of pentose and the large amounts characteristic of pentosuria. It is apparent that essential pentosuria can be distinguished from all the above conditions by the demonstration of a chronic excretion of gram amounts of the chemically identified pentose, *L*-xylulose.

FREQUENCY

Pentosuria is without doubt uncommon, so that its occurence in more than one sib of a family indicates its familial nature. But there are two quite different estimates of the frequency of pentosuria in the population. Greenwald (1922), and later Margolis (1929), enumerated the urine examinations reported by various workers and the number of pentosurics found. There was a total of about 20 cases from 20,000 urines examined, for an incidence of one in 1,000. It is probable that the population examined had an unusually high percentage of individuals in whom some defect of metabolism was suspected. A less selected population was the nearly 131,000 applicants for life insurance and company employees whose urines were examined over a period of one and one half years (Larson, *et al.* 1937). Thirty-one individual cases of pentosuria were found for an incidence of 1 in 4,000. But approximately 11 urinalyses were made by the field medical examiners of the same company for each urinalysis made in the home laboratory. When this is taken into consideration the incidence of pentosuria would appear to be 1 in 50,000. Only urines containing 0.25 per cent or more reducing substance ("1+" or "2+" Benedict reactions) were tested for pentose in this study, and since pentosuria of 0.1 per cent is not uncommonly reported, the incidence was probably underestimated. It should be noted that the incidence of pentosuria found in studies of this type should be proportional to the percentage of Jews in the population examined. The true incidence must lie somewhere between 1 in 5,000 and 1 in 50,000 people.

The identification of one "non-pentosuric" subject who normally excreted traces of xylulose (60 mg. compared with less than 1 mg. per day by controls), suggests that the incidence of pentosuria might be greatly increased if sufficiently sensitive methods were used for its detection (Touster, Hutcheson, and Rice, 1955). The existence of such individuals clearly separated from the normal individuals on the one hand and from chronic pentosurics on the other could indicate an "incompletely recessive" gene for pentosuria manifested in the heterozygous individuals as has been found for cystinuria (Harris, Mittwoch, Robson, and Warren, 1955).

Pentosuria has been diagnosed at all ages after early infancy and there is no doubt

that it is a life-long abnormality at least after the first two years of life. The youngest patients on which the diagnosis had been made were children of 18 months (Garrod, 1923) and 20 months (Protas, 1934). It may not be surprising that earlier diagnoses remain unreported since the occasions for tests by which this symptomless disorder could be recognized would rarely occur in early infancy. On the other hand, the anomaly might appear only after a certain stage of biochemical maturation. Lack of information of this type is unfortunate. Even if the condition were not strictly congenital, this would not lessen the case for its genetic control.

HEREDITY

The familial occurrence of pentosuria was noted after the first few cases were discovered. Nine of the nineteen cases collected by Janeway occurred among the sibs of four families. Garrod (1909) contented himself with observing that "evidence is accumulating of the occurence of pentosuria in brothers and sisters, and no evidence of its transmission from parent to child has yet been recorded." By 1923 Cammidge and Howard (1920) had observed a father and son in a Greek family and an uncle and nephew in a Jewish family, all with pentosuria. For only one of these, the uncle, was chemical evidence presented that the sugar was *DL*-arabinose. Greenwald (1922) favored multiple causes of the several varieties of pentosuria which might exist, while Margolis (1929) was convinced of a marked hereditary factor, more because of the high incidence among Jews, than because of familial occurrence. Lasker, Enklewitz, and Lasker (1936) published the only serious genetic analysis of pentosuria, a study of twenty pentosuric families. They cited the occurence of pentosuria in two generations of the two families reported by Cammidge and Howard. Reference was made to other published pedigrees showing two affected great aunts and a great uncle of one propositus and four children and a grandmother affected in another family. Other familial instances of pentosuria occurred only among sibs, except in one of their families.

The genetic study of Lasker *et al* was wisely restricted to the pentosuric families observed by them and proved to excrete *L*-xylulose. No instances of arabinosuria were encountered. The twenty families examined contained 37 pentosurics. Ten of these were new cases found among 34 brothers and sisters of pentosuric propositi. The disease was present in the children of ten families in which neither parent showed evidence of the disease. There was one instance of direct transmission from parent to child and this was also the only instance of marriage of first cousins. The ratio of affected to unaffected sibs after substraction of the propositi approximated 1 to 3. The findings were consistent with the transmission of pentosuria by a single recessive gene of relatively high frequency. The preponderance of males among pentosurics which had been observed in all studies was again observed. The suggestion by Margolis that many pentosurics were discovered at the examinations for life insurance where more males than females presented themselves was strikingly confirmed by the ratio of 31 males to 1 female that was found in the survey of life insurance applicants already described. There was no significant difference in the number of males and females among the new patients discovered from the propositi. It was concluded that the inheritance of pentosuria was most probably determined by a single autosomal recessive gene.

CLINICAL ASSOCIATIONS

It is definitely established that pentosuria is a separate entity from diabetes and shares few, if any, of its symptoms. This does not prevent the usual patient from being subjected to attempts to exclude or even to treat diabetes. Marble (1947) summarized the usual experience of the pentosuric: "Not infrequently, the sequence of events in their histories has been about as follows: sugar in small amounts has been found in the urine at a routine examination and the diagnosis of diabetes made, followed by institution of treatment with a restricted diet, with or without insulin; then with some the non-diabetic nature of the disorder has become evident because of lack of hyperglycemia, and the diagnosis of renal glycosuria or other benign glycosuria is made; and finally the correct diagnosis of pentosuria has been established following more careful study of the type of sugar excreted in the urine."

Migraine affected the patient described by Margolis (1929) and this impelled him to undertake a conscientious examination of the clinical details described in published cases. He believed there was a particular habitus found in most cases of pentosuria. This was characterized by neurasthenia in 77 per cent, a clinical catch-all which includes nervousness, fatigue, fleeting pains and dizziness; headaches, often of the migraine type, in 27 per cent of the cases; and some "vagotonic" symptoms like spastic constipation and bradycardia in a small number of the remaining cases.

Various writers have attributed such symptoms to racial temperament, or to the fear of diabetes. It is impossible to reach a decision about associated symptoms of pentosuria on the data available. Some thought should be given to a possible favorable effect of a gene which has a high frequency in a segment of the population. The mortality of 72 pentosurics followed for an average of 14.5 years per individual did not differ significantly from that predicted by the life tables (Lasker, 1955). The causes of death when known were not unusual. Pentosuria would appear to have no serious physiological effect, if any.

PHYSIOLOGICAL CHEMISTRY OF THE PENTOSES

The identification of a reducing sugar in the urine of certain patients, occurring without relationship to diabetes, was long a source of wonderment to physiologists. When the identification of the sugar was changed from the optically inactive but biologically occurring arabinose, to the optically active but relatively unknown xylulose, it then became conceivable that such a sugar might in some way arise from the body's metabolism. The relative constancy of the excretion of pentose (the amount is apparently related only to body size) provided few clues to the origin of the substance. Janeway, and Cammidge and Howard found that the pentose excretion was decreased by low protein diets or starvation and increased by high protein diets. Garrod (1923) concluded that the pentose was probably derived from the protein and that glucosamine was its most likely parent substance. Greenwald (1922) suggested one of the five-carbon amino acids as the source. The variation in the degree of pentosuria with the content of protein in the diet has not been universally confirmed, and this approach withered.

Margolis discovered that the drug, amidopyrine, caused the excretion of large,

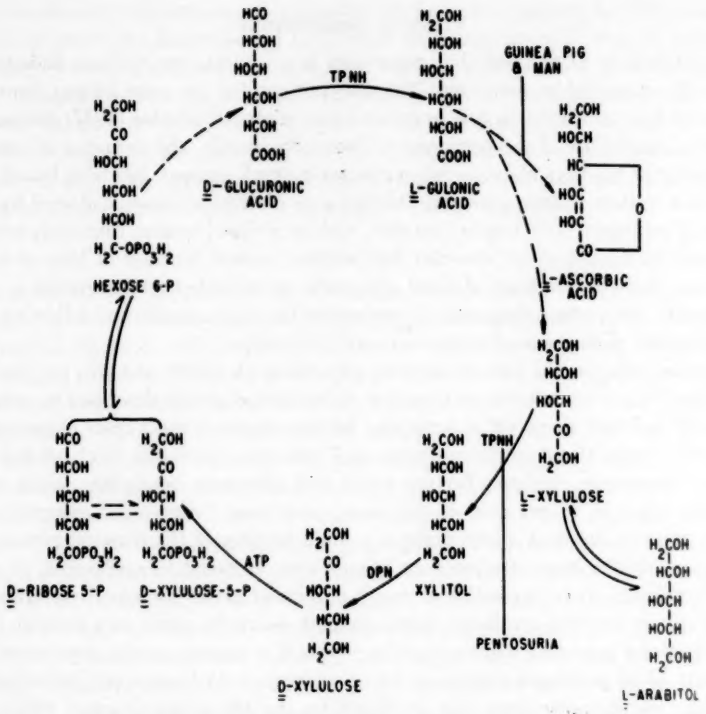

FIG. 3. Glucose-pentose cycle showing possible blocks in pentosuria (and in ascorbic acid synthesis in man).

extra amounts of pentose, at least equal in amount to the weight of drug given. This led to the eventual elucidation of pentosuric metabolism. He noted periodic increases of up to 2 g. in the amount of pentose excreted by his patient (who suffered from migraine). Eventually, he correlated the periods of increased excretion with the ingestion of amidopyrine taken to relieve the headaches. No pentose excretion followed amidopyrine ingestion by normal individuals or non-pentosuric patients with migraine. This curious but important lead has been amply confirmed (Margolis, 1929; Lasker and Enklewitz, 1933; Enklewitz and Lasker, 1935; Flynn, 1955). The extra pentose is *L*-xylulose. Enklewitz and Lasker (1935), acting on the theory that the glucuronogenic effect of amidopyrine (which is partly excreted in conjugation with glucuronate) caused the increase in pentose, found that administration of glucuronolactone itself caused extra xylulose excretion. However, it was less than half as effective as amidopyrine. Touster, Hutcheson and Rice (1955) pointed out that a gram of amidopyrine can cause the excretion of almost 2 g. of xylulose, yet less than half of the drug is excreted as the conjugated glucuronate. It is unlikely that a glucuronogenic effect could explain these results. Probably the drug inhibits some enzyme and channels hexose to pentose (and to ascorbic acid in animals (see Fig. 3)).

The possibility of controlling pentose formation to some extent led to the recognition of the place of xylulose in intermediary metabolism, but this would not have occurred had suggestions such as that of Everett (1946) been seriously considered. Since feeding glucuronic acid to normals did not lead to pentose excretion, it was suggested that the pentosuric patient had an *abnormal* enzyme system which decarboxylated glucuronic acid to yield xylulose. Similar suggestions, that xylulose could be an abnormal metabolite instead of a normal one, were also offered to explain the occurrence of homogentisic acid in alkaptonuria. Recent discoveries of pentose metabolism have demonstrated that *L*-xylulose is a normal intermediate with enzyme systems which form it and remove it (Horecker and Hiatt, 1958).

The steps of a new glucose cycle now known to occur in most tissues and involving the intermediary formation and removal of *L*-xylulose is shown in Figure 3. This series of reactions embraces those forming glucuronic acid and ascorbic acid (except in man and guinea pig where this step is blocked). *L*-xylulose is apparently formed in the course of recycling glucuronic acid to reform glucose. Attempts to determine whether the block in pentosuria was between *L*-xylulose and xylitol or between xylitol and *D*-xylulose (the enzymes for both steps are known (Hollman and Touster, 1957)), led to the discovery that *L*-arabitol was also excreted by pentosurics (Touster and Harwell, 1958). Xylitol excretion was expected if the block was located after this compound. The results do not clearly localize a metabolic block, but they suggest that if there is indeed a metabolic block in pentosuria, it is more likely to exist immediately after *L*-xylulose, as indicated in Fig. 3. The conversion of isotopically labelled glucuronolactone to labelled ribose in normal individuals, but not in pentosurics (Hiatt, 1958), demonstrated the functioning of this cucle in man and strongly supported the location of some discontinuity or block beyond *L*-xylulose in the pathway shown.

RENAL OR METABOLIC ORIGIN OF PENTOSURIA

It is known that a renal defect can account for the excretion of a metabolite in abnormal amounts and produce nearly the same picture as that which Garrod attributed to the inactivity of an enzyme. Such renal defects can be specific, life-long and determined by a single gene, the same as an enzyme defect. Cystinuria, one of Garrod's original examples of inborn errors of metabolism, as well as uric acid excretion by Dalmatian coach hounds and renal glucosuria in man are now known to occur in this way (Knox, 1958). It is necessary to see whether the renal mechanism, which has not been seriously considered for pentosuria, has been effectively ruled out. The nature of such a renal defect is the failure of a specific renal tubular transport system, so that after a substance is filtered out of the blood stream by the glomeruli, along with all the other simple compounds present, it is not reabsorbed by the tubule for conservation in the body. The exceedingly large volume of blood filtered each day and then concentrated by water reabsorption means that the urine of one day may contain some grams of the substance, even though its level in the plasma is always very low. In contrast to a metabolic block, in which the substance accumulates in the body to levels which overflow the kidney's capacity to conserve it, the blood level of the substance in a primary renal defect will be normal or low instead of elevated. Given the same blood level of the substance,

more will be excreted in the urine if there is a renal defect than if there is an enzyme deficiency. The renal defect does not prevent the metabolism in the body of that fraction of the substance which escapes filtration through the kidney. Some experimental data in the literature bear on these points of differentiation between a metabolic and a renal defect in pentosuria.

Garrod (1909) described the administration of arabinose to a pentosuric. Since no extra pentose was excreted following an oral dose of *L*-arabinose, it was apparent that the pentosuric could metabolize this sugar while he was at the same time excreting a pentose. Garrod referred to the similarities between this result and that obtained in cystinuria. The explanation for the latter condition is now known. It is a renal defect and not a metabolic block. Fischer and Reimer (1930) demonstrated that there was also no difference between normals and pentosurics in the amounts of xylose found in the blood or urine after an oral dose of xylose. Very little was excreted in either type of individual, and then only when the blood level was over 60 mg. per cent, which must be the approximate "renal threshold" for xylose. The coexistence of renal glucosuria with an easily evoked xylosuria in one patient has already been mentioned (Dunsky & Lawence, 1947), but this would be expected to occur in all renal glucosurics, if looked for, since the same renal transport system handles xylose and glucose. However, it is now clear that neither arabinose or xylose is excreted in essential pentosuria. Their metabolism and renal physiology may not be relevant to what happens to xylulose.

Greenwald (1931) could not get any of his four pentosurics to take xylulose as part of an experiment, and had to content himself with the demonstration that dogs readily metabolized this pentose excreted by pentosurics. Enklewitz and Lasker (1933) were more persuasive. Five grams of *L*-xylulose isolated from pentosuric urine was fed to a pentosuric and caused only 0.5 g. of extra pentose excretion. None was excreted by a normal control individual after the same dose. This result makes it clear that a pentosuric can metabolize *L*-xylulose almost as effectively as can normal individuals, assuming equal abilities to absorb the sugar.

The crucial information, short of measurements of the renal clearance of *L*-xylulose in normal and pentosuric individuals, is the blood level of xylulose. It is apparently quite low. Flynn (1955) was able to detect it chromatographically only by heavily loading the deproteinized plasma from a pentosuric onto the paper. The amount present was increased after a dose of glucuronolactone which increased the excretion of xylulose. Such a rise after administration of a precursor is compatible with either mechanism for the disease. Unfortunately, no attempt was made to see if xylulose in the plasma of a normal individual was more or less than in the pentosuric. If it could be assumed that there normally must be moderately high levels of xylulose in the blood before it is excreted, as is true for xylose, glucose and a number of other sugars, then it could be deduced from the data of Flynn and that published by Fischer and Reimer (1930) that pentosuria occurred because of a renal defect. In the latter experiments pentose, as measured by a method that would have included xylulose, was undetectable in the plasma of either normal or pentosuric individuals (the fasting values before xylose tolerance curves).

There is not now sufficient evidence to identify pentosuria as the failure of a

specific renal transport system for xylulose, but this possibility has not yet been excluded. It remains a reasonable possibility which must be tested directly, even with the evidence for a metabolic block recently presented by Hiatt (1958). This failure of labelled glucuronolactone to give rise to labelled ribose in a pentosuric may have alternate explanations not now apparent.

CONCLUSION

Pentosuria research has not been unusual, in comparison with the studies of the three other hereditary diseases singled out by Garrod, in the confusion which has masked the real advances. Critical evaluation of the work accumulated in the fifty years after pentosuria was called an inborn error of metabolism reveals it to be a disease entity whose main properties are well-established. There remain some uncertain questions on which further observation would be desirable, and the paramount question of a renal or an enzymic mechanism is still to be decided. The possible occurrence of arabinosuria, though it would be a separate entity if it exists at all, can now be readily determined by chromatography of the urine of all pentosurics. This is the procedure of choice for diagnosis, in any event. A more intensive study to identify any frequently associated but probably minor abnormalities is clearly indicated. The possibility of some selective advantage which the heterozygotes of pentosuria may possess has also been raised. Identification of the heterozygotes, which may be possible if the individual who excreted several hundred mg. of xylulose was one, would simplify this study and would also provide some measure of the gene frequency of this disease, which is apparently quite common among the Jewish population.

Some dissatisfaction with the utility of Garrod's concept of the inborn errors of metabolism might be voiced on the basis of the fragmentary and uncertain descriptions of these diseases commonly available. The current reviews (Knox, 1958) of the four diseases first singled out by Garrod (1908) show that, on the contrary, there is no ground for criticism. The concept of a specific functional protein under hereditary control has guided two generations of investigators to reach at last some understanding of each of the disease mechanisms. Any deficiency in the subject must instead be attributed to the oftentimes shallow and uncritical consideration which these diseases have received in the medical literature. The strength and fertility of Garrod's concept of the inborn errors of metabolism is also manifested by its continued utility in medicine and science. This has been shown by the intensive study the first four diseases have received, and by the adoption of the same hypothesis in that signal advance in physiological genetics called the "one gene—one enzyme" hypothesis. The continued addition of new disease entities also has proved that the slightly modified concept of Garrod embraced an etiologically distinct group of diseases. Fifteen years after his Croonian Lectures, Garrod (1923) added porphyria and steatorrhea (now separated into idiopathic steatorrhea and cystic fibrosis of the pancreas) to the original four inborn errors of metabolism. The mere enumeration of those since added to the list by others would serve no useful end. It is long and rapidly growing longer. The original concept, now modified to admit the hereditary control not only of enzymes, but also of other functional proteins such as the discrete

renal transport systems, the hemoglobins, the blood cell antigens and the plasma proteins, covers all of those many conditions which are best called the hereditary molecular diseases, and in which all clinical aspects of the disease can be referred to the hereditary molecular defect of one species of protein.

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A Study of Major Congenital Defects in Japanese Infants[1]

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DURING THE COURSE of a study on the potential genetic effects of the atomic bombs (Neel and Schull, 1956), considerable information was accumulated concerning congenital malformations occurring among Japanese births. In view of the current and increasing interest in the subject of congenital defect, a detailed presentation of the material seems worth while. The data provided by this study make it possible to compare for the first time many aspects of the congenital malformation problem in Caucasian and Mongolian populations, with results that lead to certain conjectures concerning the biological significance of human congenital malformations.

I. ASCERTAINMENT OF MATERIAL

Between 1948 and 1954, 81,477 pregnancies were registered in Hiroshima, Nagasaki, and Kure (a control city), in connection with the Genetics Program of the Atomic Bomb Casualty Commission (ABCC). Registration could occur at any time following the twentieth week of gestation, and was approximately 90–95 per cent complete during the period of this study. The mean interval between registration and termination was 16 weeks, 2 days in Hiroshima and 16 weeks, 6 days in Nagasaki. The circumstances under which pregnancies were registered have been described in detail elsewhere (Neel and Schull, 1956). Because of the stage in pregnancy at which registration was effected, and the degree of completeness of registration, the present series should be relatively free of the biases which sometimes creep into studies of this nature. Among the 81,477 pregnancy terminations studied, three categories of terminations have been excluded from the present analysis:

1.) All terminations in which one or both parents, on the basis of their experience at the time of the atomic bombings, fall into our radiation categories 3, 4, and 5 corresponding respectively to estimated mean radiation doses of 50–100 *roentgen*

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equivalents physical (*rep's*), 100–150 *rep's*, and 200–300 *rep's*. Although no significant effect of radiation on malformation frequency was observed, it has seemed advisable, to avoid possible criticism concerning the composition of the material, to eliminate these pregnancies from the series.

2.) All terminations for which the parents were known to be consanguineous; the findings in this group will be presented in separate papers (Schull, 1958; Morton, 1958).

3.) A miscellaneous group of terminations, itemized in detail in Table 6.1 of Neel and Schull (1956), in which the basis for the exclusion was for the most part either incomplete information or an artificial interruption of pregnancy.

There are left a total of 64,569 births, the material on which this paper is based. Of these, 56,252 were single births in Hiroshima and Nagasaki and are the same births as are entered in the appropriate cells of Tables 7.1, 8.6, and 8.7 of Neel and Schull (1956). An additional 7,544 of these births were single births studied in Kure. With respect to this latter group, at the outset of the Genetics Program it was felt that the significance of the observations to be made in Hiroshima and Nagasaki would be enhanced by the use of a control city and Kure, a former naval base and shipbuilding center some 20 miles from Hiroshima, was selected for this purpose. It subsequently became apparent that because of migration into Hiroshima and Nagasaki following the war, as well as the return of demobilized members of the military, control material could be found within the two cities, and for this reason the use of a separate control city was abandoned after two and one-half years (1948–1950).

Finally, the material contains 773 infants resulting from multiple births. The findings in the children resulting from single and from multiple births will be presented in separate sections, because of the relevance of the latter to some of the genetic problems to be discussed later.

II. THE PATTERN OF CONGENITAL MALFORMATIONS IN SINGLE BIRTHS, AS REVEALED BY CLINICAL EXAMINATION SHORTLY AFTER BIRTH

Inasmuch as it is one purpose of this paper to supply normative data with respect to the congenital malformations to be observed in Japan, it is advisable to describe briefly the exact provisions for the diagnosis of congenital malformation in this series. Approximately 90–95% of these births were attended by a midwife, the remaining being attended either by a physician or an unregistered attendant. The individual in attendance completed a brief form supplied by the ABCC (The Genetics Short Form, Neel and Schull, 1956, pp. 6–7), which included an item concerning the occurrence of congenital malformation. If a congenital malformation was noted to be present, this information was at once made known to the ABCC, and a physician employed by the latter examined the infant as soon as possible, usually within 24 hours of receipt of the information. If the child appeared normal, this fact was reported on a more leisurely schedule; but again, usually within the first ten days of life, the infant was examined by a physician employed by the ABCC. If the physician encountered a clear-cut malformation, he described this on a special form (The Genetics Long Form, Neel and Schull, 1956, pp. 10–13). If there was doubt con-

TABLE 1. THE KINDS OF MALFORMED INFANTS OBSERVED AMONG SINGLE BIRTHS IN THE CITIES OF HIROSHIMA, NAGASAKI, AND KURE, JAPAN, BETWEEN THE YEARS 1948 AND 1954

Type of Malformation	Hiroshima	Nagasaki	Kure	Total
I. *Single malformations*				
A. *Musculoskeletal system*				
Absence of radius with oligodactyly			1	1
Absence of radius with syndactyly		1		1
"Amputation," congenital, of fingers, with constrictions of fingers	1	1		2
Arthrogryposis multiplex congenita	1			1
Brachydactyly		1		1
Club foot (all types)	19	27	13	59
Club hand		1		1
Diaphragmatic hernia	1			1
Dislocation of hip	8	7	1	16
Exostosis of bone		1		1
Hemimelus	1	1		2
Inguinal hernia (females only)	25	15	2	42
"Lobster claw" deformity of hand		1		1
"Lobster claw" deformity of foot; syndactyly		1		1
Maldevelopment, right hand, with syndactyly and congenital amputation of fingers	1			1
Oligodactyly	2	3		5
Oligodactyly; syndactyly; absence of right tibia & astragalus	1			1
Polydactyly-syndactyly complex:				
Polydactyly	11	22	5	38
Polydactyly-syndactyly	8	2	1	11
Syndactyly	3	5	4	12
Subluxation, knee		1		1
Ventral hernia		2		2
B. *Respiratory system*				
Lung, aplasia, or hypoplasia	1			1
C. *Cardiovascular system*				
Congenital heart disease, type undetermined	36	48	5	89
D. *Hemic and lymphatic systems*				
Cystic hygroma	3	3		6
E. *Digestive system*				
Atresia ani	3	2		5
Atresia ani with rectovaginal fistula	1	1		2
Gastroschisis	1		1	2
Harelip-cleft palate complex:				
Harelip, with or without minor cleft of gum	25	25	4	54
Harelip and cleft palate	38	23	5	66
Cleft palate, without harelip	17	11	1	29
Intestinal obstruction	1	1		2
Macroglossia (?lymphangioma)	1	1		2
Omphalocele	2			2
F. *Urogenital system*				
Hypospadias	2	3	2	7
"Micropenis" (?hypospadias)	1			1

TABLE 1—*Continued*

Type of Malformation	Hiroshima	Nagasaki	Kure	Total
G. *Nervous system*				
Anencephaly	16	16	2	34
Cranioschisis with encephalocele	1			1
Hydrocephaly	5	5	1	11
Microcephaly	1	2		3
Myelodysplasia	1			1
Nystagmus		1		1
Spina bifida, with or without club foot:				
Simple		5	1	6
With meningocele	1	1		2
With myelomeningocele	1	2		3
H. *Organs of special sense: eye*				
Anophthalmos-microphthalmos complex:				
Anophthalmos	1	3		4
Anophthalmos-microphthalmos	1	1		2
Microphthalmos	6	1		7
Blepharophimosis	1			1
Cataract		2		2
Coloboma iridis		1		1
Corneal opacity (non-luetic)		4	1	5
Ptosis		1		1
I. *Organs of special sense: ear*				
Ear malformation, complex	4	5		9
Microtia	1			1
Polyoty	1			1
J. *Integumentary system*				
Anonychia, partial	1			1
Congenital ectodermal defect	1			1
Defect in scalp & occipital bones (congenital avulsion of scalp)	1			1
Ichthyosis congenita	1	1		2
Leukoderma, partial	1			1
Multiple subcutaneous tumors, ?type		1		1
II. *Multiple defects involving several systems*				
Anencephaly				
With anophthalmos			1	1
With cleft palate	1			1
With harelip and cleft palate	1			1
With harelip and cleft palate; polydactyly	1			1
With harelip and cleft palate; omphalocele; club foot		1		1
With tumor, hand, type undetermined		1		1
Atresia ani et vaginae				
Alone		1		1
With polydactyly	1			1
Atresia ani				
With harelip and cleft palate		1		1
With harelip and cleft palate; hypospadias		1		1
With hypospadias			1	1
With oligodactyly; absence of left radius	1			1
With polydactyly and syndactyly		1		1

TABLE 1—*Continued*

Type of Malformation	Hiroshima	Nagasaki	Kure	Total
Cleft palate				
With dislocation of hips	1			1
With hypoplasia of mandible, microglossia	2			2
Club foot; absence of radius, bilateral, with camptodactyly	1			1
Club foot; aplasia of right radius, and oligodactyly		1		1
Club foot; dislocation of hip		2		2
Club foot; pterygium colli; malformation of ear		1		1
Club foot and hands; malformation of ear	1			1
Club foot and oligodactyly	1			1
Congenital heart disease, type undetermined:				
With cavernous hemangioma		1		1
With cervical tumor, type undetermined	1			1
With corneal opacity	1			1
With funnel chest		1		1
With inguinal hernia	1			1
With harelip and blepharophimosis	1			1
With malformation of ear; ?early hydrocephaly			1	1
With polydactyly		1		1
With cleft palate; polydactyly		1		1
With syndactyly; brachydactyly	1			1
Cranioschisis with meningocele; congenital heart disease, type undetermined	1			1
Cranioschisis with meningocele; malformation of ear	1			1
Cranioschisis with meningoencephalocele; complex malformation, both upper extremities; syndactyly	1			1
Harelip; ?early hydrocephaly			1	1
Harelip and cleft palate:				
With anophthalmos; polydactyly		1		1
With arhinia		1		1
With arhinia; hydrocephaly		1		1
With club hand; oligodactyly		1		1
With club foot	2			2
With hypospadias; malformation of thumb; malformation of ears	1			1
With polydactyly; malformation of ears			1	1
Hydrocephaly; microtia	1			1
Microphthalmos and anophthalmos; arhinia	1			1
Omphalocele:				
With atresia ani; club foot		1		1
With extrophy of bladder			1	1
With harelip; polydactyly; hypospadias		1		1
With polydactyly	1			1
Polydactyly; corneal opacities		1		1
Spina bifida with meningocele, club foot; malformation of ears; probable hypospadias	1			1

TABLE 1—*Continued*

Type of Malformation	Hiroshima	Nagasaki	Kure	Total
Spina bifida, cervical, with meningomyelocele; cleft palate; absence of right radius and thumb			1	1
III. *Complex malformations*				
No diagnosis	1	1		2
Pygomelus (probable)	1			1
Situs inversus		2		2
Status Bonnevie-Ulrich		1		1
Teratoma, sacral	1	2		3
IV. *Syndromes*				
Achondroplasia	1	6	1	8
Mongolism	2	4		6
Polyostotic fibrous dysplasia(?)		1		1
V. *Ill-defined states*				
Tumor, abdominal, type undetermined	1			1
Total	293	300	58	651
No. of births	26,012	30,240	7,544	63,796
Rate	0.0113	0.0099	0.0077	0.0102

cerning the nature or extent of the malformation, an effort was made to bring the child to the facilities of the ABCC where, in a "Verification Clinic," he was seen by both Japanese and American pediatricians, and any X-rays, etc., necessary to a diagnosis were obtained. With respect to the possibility of certain diagnoses, such as a borderline hydrocephalus at birth, a child might be seen in the Verification Clinic on several different occasions.

The findings resulting from this procedure are shown in Table 1. Caution is indicated in the uncritical use of these figures for normative purposes. There is, on the one hand, a group of malformations readily diagnosable at birth under almost any conditions. This group includes such defects as anencephaly or harelip. There is, on the other hand, a group of defects diagnosed only with great difficulty if at all at birth, such as severely defective vision or hearing, or neurological deficit. Finally, there is a group of defects, such as congenital heart disease or congenital dislocation of the hip, where a fraction may be readily diagnosable at birth, but really accurate figures are difficult to obtain until the children being surveyed have reached their first (or even a later) birthday. It is felt that of the defects listed in Table 1, the following seven in particular are so readily diagnosed and sufficiently frequent that their incidence may with meaning be compared with the findings in other extensive series in the literature: anencephaly, spina bifida manifesta, harelip with or without cleft palate, isolated cleft palate, atresia ani, anophthalmos-microphthalmos, and polydactyly.

No entirely satisfactory classification of congenital abnormalities has yet been devised. In Table 1, the unit of entry is the malformed child; each child, regardless of the number of malformations, has been entered in the table only once. For purposes of convenience, children with defects largely confined to one system have been listed first, then children with multiple defects involving two or more systems

are listed, the most "important" defect from the standpoint of survival being listed first as a convention. In some instances, the decision as to the more important defect was somewhat arbitrary. The relatively few children with highly complex malformations, "syndromes," or ill-defined conditions, are listed last.

A number of relatively minor defects observed in the newborn population have not been included in the listing. Among these are hydrocele, umbilical hernia, small hemangiomas and papillomas, auricular pits, or incompletely descended testicles at birth. Some of these, if persistent, might deserve the appellation of major defect, and, as will become apparent, if certain of these defects were observed in the series of children re-examined at age nine months (see below), they were in fact treated as major malformations. A word should be said concerning the occurrence of congenital heart disease and congenital dislocation of the hip in the listing. The diagnosis of congenital heart disease at birth is notoriously unreliable, and for this reason, only the relatively few cases of cyanotic congenital heart disease were included in the malformations utilized in the analysis of the potential genetic effects of the atomic bombs. The criteria for inclusion in the present listing are less stringent, consisting, aside from persistent cyanosis, of a grade III or IV apical systolic murmur present on repeated examinations, a precordial thrill, and/or cardiomegaly in the absence of another adequate explanation. From the findings at age nine months to be discussed later there can be no doubt that many cases of congenital heart disease were missed in this examination; the figures are given solely as an index of what this type of examination at this age level may be expected to reveal. Minor degrees of congenital dislocation of the hip often do not become apparent until the child attempts to walk; the figure given here was also shown by the findings of the examination of a random sample of this same series at age 9 months to be an underestimate. The criteria of diagnosis consisted of marked shortening of one extremity with asymmetry of the skin folds and/or external rotation of the extremity, or an unquestionably positive response to Ortolani's maneuver, i.e., a click detected in the hip during passive abduction of the thigh. In almost every instance, there was X-ray confirmation of the diagnosis.

The congenital malformations listed in Table 1 are the malformations responsible for the entries in the appropriate cells of Tables 8.6 and 8.7 of Neel and Schull (1956), plus the malformations observed among single births in Kure, plus 88 cases of congenital heart disease not scored in the analysis of the genetic effects of the atomic bombs but included here with the reservations mentioned earlier. Four malformed infants earlier excluded for technical reasons (item 3 p. 399) were on reconsideration found suitable for inclusion in this series. The frequency of major congenital defect in this series is 1.02 per cent. In the course of preparing Table 1, one minor medical error in the earlier (1956) tabulation came to light. Infants for whom the sex was not recorded were automatically rejected from consideration in the analysis of the data concerning the effects of the atomic bombs. Included among the material was one infant born in Hiroshima with sympodia, atresia ani, and no classifiable external genitalia. Autopsy revealed absence of the genitourinary system. This was coded as "sex unrecorded"—whereas it was actually "sex unrecordable." Inclusion of this infant in the table would not alter the percentages given there.

The frequency of malformed infants appears to be significantly lower in Kure than in Hiroshima and Nagasaki ($\chi^2 = 7.711$, d.f. $= 2$, $P < .05$). However, in the material as a whole, there was a tendency for somewhat more malformations to be diagnosed in the later than in the earlier years of the study (cf. Neel and Schull, 1956, p. 70). Since the data from Kure were collected only during the first three years of a six-year study, it seems doubtful whether this difference between Kure and the other two cities is of any significance.

It will be apparent that certain of the diagnoses entered in Table 1 do not carry the precision desirable in a contemporary study of congenital malformations. It should be recalled that the great majority of these births occurred at home rather than in a hospital. The ambiguous diagnoses represent, for the most part, 1) stillborn infants or infants dying shortly after birth, where the body was disposed of before examination by an ABCC physician, and only a midwife's report was available, or 2) instances where the home visit proved unsatisfactory as a basis for diagnosis, and for a variety of reasons, it was not possible for the child to be seen in Verification Clinic.

Any comparison of the frequency of major malformation in this series with the frequency in other series is handicapped by the fact that no two series on major congenital defect have been assembled in precisely the same fashion. The only other extensive Japanese series known to the author is that of Mitani (1943; see below), in which among 49,645 births the frequency of major defect, exclusive of congenital heart disease, was 0.92 per cent, a satisfactory agreement with the present series. Among relatively recent Caucasian series which appear more or less comparable to the present, the over-all frequency of major defect has been as follows: Malpas (1937)—2.11 per cent of 13,964 (England); Naujoks (1938)—1.33 per cent of 17,800 (Germany); Newton and McLean (1947)—0.84 per cent of 15.421 (U.S.A.); Nowak (1950)—1.11 per cent of 21,384 (Germany); Aresin and Sommer (1950)—0.91 per cent of 43,647 (Germany); Hegnauer (1951)—0.67 per cent of 141,706 (Germany); Worm (1952)—1.01 per cent of 14,611 (Germany); Coffey and Jessop (1955)—1.63 per cent of 12,552 (Ireland). In this listing there has been no attempt to be exhaustive, but the series quoted are probably representative. In general, the total frequency of major defect appears to be quite similar in Japanese and Caucasian infants.

It should be noted that the present series does not include multiple births, whereas the other series all do. Since, as will be shown later, the frequency of major defects among multiple births does not differ from that among single births, this fact is not thought to influence the validity of the comparison.

No series concerned with native Africans is known to the author. Among those series assembled in the United States composed of both live and stillborn Negro and Caucasian infants, the frequency of gross defect appeared to be somewhat lower in Negro infants in the material of Hirst (1945), but somewhat higher in the series of McIntosh *et al* (1954). Although the birth registration practices of certain states provide some data on this point, the validity of any difference which might be reported from studies of birth certificates is rendered doubtful by the possibility of greater underreporting for Negro than white infants. However, death certificates

TABLE 2. FREQUENCY OF OCCURRENCE OF SIX READILY DIAGNOSED MALFORMATIONS IN JAPANESE AND CAUCASIAN BIRTHS

Population	Location	Investigator	No. of births	Defect												Total Dx.	Dx. per 1000 children
				anencephaly		spina bifida		anoph-microph-thalmos		atresia ani		harelip-cleft palate		polydactyly			
				no.	incidence	no.	incidence	no.	incidence	no.	incidence	no.	incidence	no.	incidence		
Japanese	This series	This series	63,796	40	0.00063	13	0.00020	16	0.00025	15	0.00024	171	0.00268	59	0.00092	314	4.92
	Tokyo	Mitani, 1943	49,645	33	0.00066	11	0.00022	10	0.00020	15	0.00030	94	0.00189	57	0.00115	220	4.43
		Total	113,441	73	0.00064	24	0.00021	26	0.00023	30	0.00026	265	0.00234	116	0.00102	534	
Caucasian	England	Malpas, 1937	13,964	44	0.00315	39	0.00279	0	—	4	0.00029	17	0.00122	16*	0.00115	120	8.59
	Switzerland	Ehrat, 1948	50,147	27	0.00054	54	0.00108	6†	0.00012	20	0.00040	74	0.00148	20	0.00040	201	4.01
	U.S.A.	Lucy, 1949	11,881	13	0.00109	15	0.00126	0	—	1	0.00008	15	0.00126	9	0.00076	53	4.46
	Sweden	Böök, 1951	44,109	24	0.00054	47	0.00107	4	0.00009	19	0.00043	77	0.00175	30	0.00068	201	4.56
		Total	120,101	108	0.00090	155	0.00129	10	0.00008	44	0.00037	183	0.00152	75	0.00062	575	

* Entered as "malformed hands and arms;" undoubtedly includes more than polydactyly.

† The author lists 12 cases of "Missbildungen des aüsseren Ohres, der Nase, der Augen." On the basis of our experience in Japan, it has been estimated that not more than half of these fall into the anophthalmos-microphthalmos category. This rough approximation, made necessary by the grouping of the data, probably fixes the upper limit of the frequency of the defect.

would seem to be somewhat less subject to bias than birth certificates, although this is a point on which it is difficult to form an opinion.

Utilizing death certificates, Smith (1956), on the basis of special tabulations by the National Office of Vital Statistics, has supplied important data concerning the reported frequency of *fatal* congenital malformations among American citizens of Japanese descent living in the United States and Hawaii, in comparison with their frequency in white and non-white (95 per cent Negro) populations. The correspondence between the rates of Americans of Japanese descent and Caucasian Americans is noteworthy; rates for non-whites are somewhat (but nonsignificantly) lower. This may be a function of the size of the series, since other studies based on vital statistics records involving only a white:non-white comparison show that fatal congenital malformations are reported significantly less frequently in non-whites than in whites (National Office of Vital Statistics, 1956; World Health Organization, 1956; see also Murphy, 1947). It is a point to be returned to later, that among the 17 broad causes of death whose frequencies Smith (1956) compared for Japanese Americans, American Negroes, and American Caucasians, only for congenital malformations and diseases of the blood-forming organs were there no significant differences among all three groups. While final conclusions are impossible, in general, and particularly considering the variability in the relative frequency of other disease entities, the frequency of congenital malformations seems rather comparable for the main racial groups, with the possibility that Negro frequencies, especially with respect to potentially fatal malformations, may be slightly lower than those of the other two racial groups discussed.

We turn now to a consideration of the frequency with which various specific defects occur in the Japanese material, as contrasted with material based on Caucasian and Negro births. Table 2 gives the frequency in six different series of six specific defects, either occurring alone or in combination with other defect. In this table, the unit of entry is no longer the malformed child, but the specific defect. Thus a child with a harelip and polydactyly would be listed twice in the table. It had originally been hoped to include in the table a breakdown as to whether the specific defect occurred alone or in combination with other defect, a point of considerable epidemiologic significance, but although this information can be extracted from Table 1 for the Japanese data, the literature on abnormalities in Caucasian populations is unfortunately not presented in such a manner as to make this possible. The six specific defects selected for inclusion in Table 2 were chosen because their diagnosis appears to present a minimum of ambiguity and because they are sufficiently common that significant figures are available. Conditions such as congenital hydrocephalus, dislocation of the hip, club foot, or heart disease, by contrast, were not thought to present meaningful material for comparison, since the subjective element in diagnosis is relatively great. On the other hand, such clear-cut conditions as omphalocele or congenital "amputations" are not sufficiently common to provide enough material for comparative purposes in series of the size usually compiled.

As noted above, there apparently exists only one other extensive series of this nature concerned with births in Japan, that of Mitani (1943). His findings with

respect to the six specific defects here under scrutiny are given in Table 2. This series was compiled in the Tokyo Red Cross Maternity Hospital, and for this reason, in view of the small proportion of Japanese births occurring in hospitals, might be expected to involve some selection with respect to the complications of pregnancy, some of which, such as hydramnios, are associated with congenital malformations (Prindle, Ingalls, and Kirkwood, 1955). It will be noted that the agreement between the two series is actually quite good, with the exception of harelip and cleft palate (see below).

It would be desirable to treat harelip with or without cleft palate separately from isolated cleft palate, because of Fogh-Andersen's (1943) evidence that from the standpoint of etiology they may represent separate entities. Unfortunately, in some of the otherwise best series on Caucasian births these two defects have apparently been included under the same heading. They are therefore grouped in Table 2, but will be considered separately in a later section.

Considerable difficulty has arisen in finding in the literature *comprehensive* series dealing with congenital malformation among Caucasian births in which the findings are presented in sufficient detail to permit meaningful comparisons with the two Japanese series. The principal problems which arise when one attempts to make comparisons may be grouped under the following headings:

1. *Selection of material.*—Most series are either based on a hospital experience or a perusal of vital statistics. Hospital series are open to the question of bias, although, on the basis of the agreement between the two series from Japan, the bias may not be so great as has previously been thought. On the other hand, there may be gross underreporting of congenital malformation where this information is requested on a birth certificate (cf. Lilienfeld, Parkhurst, Patton, and Schlesinger, 1951). This underreporting is undoubtedly more marked for some classes of defects than for others. For example, anencephaly and spina bifida manifesta are probably better reported than isolated cleft palate or polydactyly. In the comparisons in Table 3, we shall rely principally on hospital series, as presenting the lesser of two statistical evils. A second type of selection which enters into the composition of many series is based on viability, some series dealing only with defective infants who were either stillborn or died during a stated period (e.g. Murphy, 1947), others only with liveborn (e.g., Harris and Steinberg, 1954). While such selection is of course valid for certain purposes, it cannot result in normative material for the population as a whole. A third and final type of selection which should be mentioned is based upon where the dividing line is drawn between major and minor malformation. For instance, in two series, otherwise suitable for inclusion in Table 2, there appears no mention of polydactyly (Newton and McLean, 1947; Coffey and Jessop, 1955). In view of the frequency of this defect, it appears much more likely that it was disregarded in the compilation of the series than that it failed to occur. Although these two series remain useful for a variety of comparisons, this apparent omission renders them unsuitable for the type of statistical treatment to which Table 2 is to be subjected.

2. *Grouping of material.*—Numerous authors—presumably motivated in part by a desire to meet editorial requirements—have resorted to groupings which may

consolidate their lists but may at the same time obscure biological relationships. For instance, 10 per cent of the 483 verified malformations in the otherwise excellent study of Stevenson, Worcester, and Rice (1950) are listed simply as "multiple deformities." There also appear on their listing such items as "anencephalus and other deformities" and "hydrocephalus and other deformities," thus rendering any exact tabulation impossible. A comparable difficulty arises in the series of Carter (1950), in which "where two malformations were present the child was listed under the major malformation. Where more than two were present the child was listed under multiple." As a final example of this difficulty, one may cite the paper of Wallace, Baumgartner, and Rich (1953), where "if a baby had more than one malformation, the more serious condition was made the primary one, and the case so classified. The one exception to this rule was cleft palate or harelip which was given a primary priority also." While such groupings may not interfere with the primary purposes of the respective authors, they do seriously limit the usefulness of the material for students of comparative teratology. This same grouping of material has led to the exclusion from Table 3 of the series of Naujoks (1938), DePorte and Parkhurst (1945), Landtman (1948), and Nowak (1950). It is unfortunately in the more extensive (and correspondingly more valuable) series where, presumably because of space considerations, this defect tends to occur. Although some of these series will be used later for approximate comparisons, such comparisons will always be indicated as based on "incomplete" data.

3. *Occurrence of diverse racial backgrounds among the parents.*—A final difficulty to be mentioned, of especial significance in some of the series from the United States, has to do with the practice of combining, in one series, children of different racial backgrounds, specifically, "white" and "non-white." Thus, in the careful study in New York City of McIntosh *et al* (1954), where infants were if possible examined during the neonatal period and again at 6 and 12 months (and some even later), although the total malformation rate of 7.8 per cent in the children of non-white parents is said to differ significantly from the rate of 6.3 per cent in the children of white ancestry, no breakdown by ancestry is given in the tabulations. The study of Wallace, Baumgartner, and Rich (1953) from the same city, which will not be used for normative purposes because of its reliance on *live* birth certificates and because of the way in which the malformations are grouped, presents a valuable insight into the possible magnitude of the bias introduced by failure to tabulate according to ancestry. In contrast to the study of McIntosh *et al*, they note no differences in total malformation rate in relation to ancestry. With respect to specific malformations, they write: "The reported incidences of cleft palate in the white and non-white groups statistically do not differ—0.82 and 0.59 per 1,000 live births, respectively. Certain conditions seem to be higher in the white—e.g., club foot and hypospadias. For example, the reported incidence of club foot is 2.30 per 1,000 live births in the white group (320 cases) and 1.30 in the non-white (31 cases). For hypospadias, the reported incidence in the white group is 0.69 per 1,000 live births (96 cases) and 0.17 in the non-white (4 cases). No valid conclusion can be drawn as to whether this is a chance occurrence or whether there is a color differential. On the other hand, polydactylism does show a statistically significant color differ-

TABLE 3. HOMOGENEITY CHI-SQUARE ANALYSIS OF THE DATA OF TABLE 2. E = ENGLAND, Sw = SWITZERLAND, S = SWEDEN, U = UNITED STATES, J_1 = THIS SERIES, J_2 = JAPANESE SERIES OF MITANI, AND J_T = COMBINED JAPANESE SERIES. CHI-SQUARE VALUES SIGNIFICANT AT THE 5 PER CENT LEVEL ARE INDICATED BY A SINGLE ASTERISK, WHILE THOSE AT THE 1 PER CENT LEVEL ARE INDICATED BY TWO ASTERISKS

Source	DF	χ^2	Source	DF	χ^2
I. Comparison of the four Caucasian series					
E vs. U	4†	6.427	U vs. S	5	10.357
E + U vs. Sw	5	41.045**	U + S vs. E	5	38.689**
E + U + Sw vs. S	5	15.507**	U + S + E vs. Sw	5	14.285*
	14	62.979**		15	63.331**
E vs. U	4	6.427	U vs. S	5	10.357
E + U vs. S	5	43.275**	U + S vs. Sw	5	4.472
E + U + S vs. Sw	5	14.285*	U + S + Sw vs. E	5	48.755**
	14	63.987**		15	63.584**
E vs. Sw	5	41.508**	Sw vs. S	5	3.147
E + Sw vs. U	5	4.499	Sw + S vs. U	5	11.271*
E + U + Sw vs. S	5	15.507**	Sw + S + U vs. E	5	48.755**
	15	61.514**		15	63.173**
E vs. Sw	5	41.508**	Sw vs. S	5	3.147
E + Sw vs. S	5	14.226*	Sw + S vs. E	5	54.385**
E + Sw + S vs. U	5	5.538	Sw + S + E vs. U	5	5.538
	15	61.272**		15	63.070**
E vs. S	5	45.421**	E vs. U	4	6.427
E + S vs. U	5	3.141	Sw vs. S	5	3.147
E + S + U vs. Sw	5	14.285*	E + U vs. Sw + S	5	53.925**
	15	62.847**		14	63.499**
E vs. S	5	45.421**	E vs. Sw	5	41.508**
E + S vs. Sw	5	11.250*	U vs. S	5	10.357
E + S + Sw vs. U	5	5.538	E + Sw vs. U + S	5	10.123
	15	62.209**		15	61.988**
U vs. Sw	5	10.875	E vs. S	5	45.421**
U + Sw vs. E	5	35.261**	U vs. Sw	5	10.875
U + Sw + E vs. S	5	15.507**	E + S vs. U + Sw	5	5.877
	15	61.643**		15	62.173**
U vs. Sw	5	10.875			
U + Sw vs. S	5	3.430			
U + Sw + S vs. E	5	48.755**			
	15	63.060**			
II. Comparison of the two Japanese series					
J_1 vs. J_2	5	8.342			
III. Comparison of the combined Japanese series with the individual Caucasian series					
J_T vs. E	5	147.554**			
J_T vs. Sw	5	90.228**			
J_T vs. S	5	68.871**			
J_T vs. U	5	53.968**			

† No comparison on microphthalmos-anophthalmos.

ence; in the white group the reported incidence is 0.58 for 1,000 live births (80 cases) as compared with the reported incidence of 4.00 in the non-white (95 cases). This color difference is not found in adactylism or syndactylism, or in the other frequent types of congenital malformations listed in Table 2." Because of failure to specify ancestry, we shall also omit the series of Greenberg *et al* (1949).

Even with respect to the four series on Caucasian births finally utilized in Table 2 for comparative purposes, it has sometimes been necessary to make rather arbitrary assumptions. Thus, in the series of Lucy (1949), the diagnosis of simple anencephaly does not appear, but "anencephaly and spina bifida;" it is assumed this corresponds to simple anencephaly, since there is also an entry for "spina bifida." Malpas' (1937) well known series lists 12 out of 294 cases as "miscellaneous," apparently includes polydactyly under the heading of "malformed arms and hands," and is not entirely specific concerning associations of defects. Ehrat (1948) apparently groups anophthalmos-microphthalmos with major defects of the nose and ear, necessitating certain rather arbitrary assumptions.

Tables 3 and 4 present an analysis of the data of Table 2. In Table 3 the two Japanese and four Caucasian series have been contrasted in all possible ways. This contrast involves the assumption of independence of various entries. Since the same infant may be represented twice (e.g., if it had both harelip and anencephaly), this assumption is not strictly justified, but it is felt the error so introduced is negligible. It is apparent that there is considerable heterogeneity among the Caucasian series. The findings in the Swiss and Swedish series are not significantly different. The English series differs markedly from these two, largely (possibly entirely) because of the strikingly high incidence of anencephaly and spina bifida. The United States series does not differ significantly from any of the other three Caucasian series, although it does differ significantly from the pooled Swiss and Swedish sample, suggesting that if larger series were available, the differences between the series might be significant. Table 4 brings out the fact that with respect to four of the specific malformations concerned, the United States' incidence is intermediate between that in England, on the one hand, and Sweden and Switzerland, on the other hand. In view of the ancestry of the people of the United States, this has clear genetic implications, to which we shall return later.

The two Japanese series do not differ from one another, and so for the purposes of further analysis may be pooled. The pooled Japanese sample differs from each of the Caucasian samples, and, as can be seen from a comparison of the χ^2 values, to a much more significant degree than the various Caucasian series differ from one another, although the numerical inequality of the various samples must be noted in this connection. Again attention is directed to the fact that the present series is composed only of single births but that because of the similarity of the findings in single and multiple births, this does not impair the validity of the comparisons.

We will next consider briefly the relative contributions to these differences of each of the six malformations listed in Table 2. From the standpoint of comparative teratology, a comprehensive series which permits multiple comparisons between two populations is far more valuable than a considerable number of series each dealing with a single defect, since only in the comprehensive series can the correla-

TABLE 4. THE RANKING OF THE VARIOUS CAUCASIAN AND JAPANESE SERIES WITH RESPECT TO THE FREQUENCY OF SPECIFIC DEFECTS, AND A χ^2 COMPARISON OF THE FREQUENCY OF THESE DEFECTS FOR THE COMBINED JAPANESE SAMPLE AS CONTRASTED TO THE COMBINED CAUCASIAN SAMPLE. BECAUSE OF THE FAILURE TO DEMONSTRATE SIGNIFICANT DIFFERENCES BETWEEN THEM, THE SWEDISH AND SWISS SERIES HAVE BEEN COMBINED (S_T), AS HAVE THE TWO JAPANESE SERIES (J_T). THE SYMBOL C_T REFERS TO THE COMBINED CAUCASIAN SAMPLE. FOR ALL COMPARISONS THERE IS A SINGLE DEGREE OF FREEDOM. χ^2 VALUES AT THE 5 PER CENT LEVEL ARE INDICATED BY ONE ASTERISK AND AT THE 1 PER CENT LEVEL BY TWO ASTERISKS

Defect	Frequency seriation	χ^2 J_T vs. C_T
Anencephaly	$E > U > J_T > S_T$	4.919*
Spina bifida	$E > U > S_T > J_T$	88.551**
Anophthalmos-microphthalmos	$J_T > S_T > U > E$	8.058**
Atresia ani	$S_T > J_T > E > U$	1.633
Harelip-cleft palate	$J_T > S_T > U > E$	20.027**
Polydactyly	$J_T > U > E > S_T$	11.294**

tions which may throw light on etiological and epidemiological relationships be studied. Nevertheless, because of the paucity of such comprehensive series, it seems wise also to compare the present findings with those of certain series dealing with only a single defect. In addition, for limited purposes material can be selected from series which were disqualified from use *in toto* because of particular groupings of material, etc. We will refer to these as "incomplete" series. In the discussion of specific defects, "Caucasian" frequencies will frequently be contrasted with "Japanese" frequencies. Because of the differences between the various Caucasian series, the propriety of combining such heterogeneous material may be questioned. It will be noted that for four of the defects, *all* of the Caucasian series, despite their heterogeneity, exhibit either higher, or lower, frequencies than the Japanese series. Here generalizations seem justified. For two of the defects (atresia ani and anencephaly), the seriation is such that the combined Japanese sample occupies an intermediate position—here caution is certainly indicated. We turn now to a discussion of specific defects.

1. *Anencephaly.*—The extensive world literature on this subject has recently been assembled by Penrose (1957). Because of the striking nature of this defect, figures on its incidence are probably quite reliable. The incidence of the trait varies widely from locality to locality. Thus, in Northern Ireland (Belfast) Stevenson (quoted from Penrose, 1957) recorded 207 anencephalics among 30,855 births (0.00671), whereas in France (Paris and Lyon) Frezal and Lamy (quoted in Penrose, 1957) encountered only 72 cases in 204,017 births (0.00035). Moreover, there seem to be relatively more anencephalics born in winter than in summer, significant variations in incidence from year to year, and, in some regions, a trend toward fewer anencephalics in recent years (discussion in McKeown and Record, 1951; MacMahon, Record, and McKeown, 1951; Penrose, 1957). Viewed on the background of this known variability, the comparisons of Table 4 are somewhat arbitrary. Anencephaly is less frequent in the pooled Japanese than in the pooled Caucasian samples, the difference just reaching the level of statistical significance. However, the combined Swedish-Swiss sample actually shows a lower frequency than the combined Japanese, and it seems wise to adopt the provisional viewpoint

that regional differences overshadow possible racial differences to the point where conclusions concerning the latter are still hazardous.

2. *Spina bifida.*—This trait shows the greatest relative variability of any of the six under consideration. This fact notwithstanding, the frequency of the condition is clearly lower in Japanese than Caucasian births. The "incomplete" series tend to substantiate this conclusion. Thus, the frequencies of spina bifida in the series of Record and McKeown (1949), Stevenson, Worcester, and Rice (1950), and Carter (1950) were, respectively, 0.00267, 0.00196, and 0.00189.

A number of authors have stressed the etiological interdependence of anencephaly and spina bifida, largely because of the tendency of the frequencies of these two defects to show a positive correlation in different series based on Caucasian births, and the tendency towards the occurrence of both defects in the same family (e.g., Record and McKeown, 1949, 1950; MacMahon, Pugh, and Ingalls, 1953). While the general validity of this observation cannot be questioned, it is noteworthy that in the Japanese data, the frequency of spina bifida is roughly a third that of anencephaly, whereas in the Caucasian data of Ehrat (1948) and Böök (1951), with a very similar incidence of anencephaly to the two Japanese series, spina bifida is approximately twice as common as anencephaly. This would seem to imply the existence of factors capable of markedly modifying the expression of this presumed common diathesis.

3. *Anophthalmos-microphthalmos.*—The lower frequency of this defect in the Caucasian series is statistically significant. In view of the common practice of instilling silver nitrate into the eyes of all newborn infants during much of the period covered by these studies, it seems unlikely that the defect occurred but was overlooked in the Caucasian material. The defect is also not mentioned as occurring in Carter's (1950) series of 14,283 births, or Stevenson, Worcester, and Rice's (1950) series of 29,024. Sjögren and Larsson (1949), on the basis of an extensive study of the defect in Sweden, estimate its frequency at 0.000025. There seems little doubt, then, that this defect is more common among Japanese.

4. *Atresia ani.*—There is no significant difference in the frequency of this defect in the Caucasian and Japanese series. Although the average of the series given in Table 2 is slightly higher for Caucasian births, this is not borne out by the series of Moore and Lawrence (1952), Newton and McLean (1947), or Coffey and Jessop (1955), nor, with all due reservations, by the "incomplete" series of Stevenson, Worcester, and Rice (1950) and Carter (1950).

5. *Harelip and cleft palate, and isolated cleft palate.*—As noted earlier, most of the Caucasian series fail to distinguish between harelip with or without cleft palate, and isolated cleft palate, and for this reason the two defects are grouped in Table 2. The analysis of Table 4 reveals a significantly higher frequency of this defect-complex among Japanese than among Caucasian births. Table 5 is a compilation of a number of series in which the two defects have been presented separately. It appears that both types of defect tend to be more common among Japanese births. The fact that the two types of defect are, within the limits of error, increased to about the same extent lends no support to Fogh-Andersen's concept of the relative etiological independence of the two, although neither does this fact directly contra-

TABLE 5. THE RELATIVE FREQUENCIES OF HARELIP WITH OR WITHOUT CLEFT PALATE, AND ISOLATED CLEFT PALATE, IN SOME JAPANESE, CAUCASIAN AND NEGRO POPULATIONS

Population	Investigator	Number of births	Harelip ± cleft palate		Cleft Palate		Total	
			No.	incidence	No.	incidence	No.	incidence
Japanese—this series	This series	63,796	136	0.00213	35	0.00055	171	0.00268
Japanese—Tokyo, 1922–1940	Mitani, 1943	49,645	58	0.00117	36	0.00073	94	0.00189
Total		113,441	194	0.00171	71	0.00063	265	0.00234
Caucasian—Baltimore, 1895–1924	Davis, 1924	15,565	14	0.00090	3	0.00019	17	0.00109
Caucasian—Paris, 1894–1927	Peron, after Fogh-Andersen	100,889	92	0.00091	14	0.00014	106	0.00105
Caucasian—	Günther, after Fogh-Andersen	102,873	80	0.00078	22	0.00021	102	0.00099
Caucasian—Denmark, 1910–1942	Fogh-Andersen, 1943	128,306	149	0.00116	44	0.00034	193	0.00150
Caucasian—Sweden, 1927–1946	Böök, 1951	44,109	60	0.00136	17	0.00039	77	0.00175
Total		391,742	395	0.00101	100	0.00026	495	0.00126
Negro—Baltimore, 1895–1924	Davis, 1924	12,520	6	0.00048	1	0.00008	7	0.00056

dict his hypothesis. The studies of Krantz and Henderson (1947) in Hawaii indicate that the difference between Caucasians and Japanese tends to persist when representatives of the two races are living in proximity although, in view of differences in living habits, one is scarcely justified in concluding that this is strong evidence that the reason for the difference is genetic.

Attention is called to the low frequency of harelip and cleft palate in Davis' series on American Negroes (Table 5), a finding consistent with the observations of Wallace, Baumgartner, and Rich (1953) quoted on p. 409. It seems reasonably clear that with respect to the frequency of this defect, the ranking should be American Negro < Caucasian < Japanese.

6. *Polydactyly.*—The frequency of polydactyly is slightly greater in Japanese than Caucasian births. The various "incomplete" series in the literature bear out this impression. Thus, the diagnosis has a (minimum) frequency of 0.00076 in the series of Stevenson, Worcester, and Rice (1950), and 0.00049 in the series of Carter (1950). As mentioned earlier, Wallace, Baumgartner, and Rich (1953) found significantly more polydactyly in births to non-whites than to whites. The frequency seriation here would seem to be Caucasian < Japanese < American Negro. Handforth (1950) has reported a frequency of polydactylism of 0.00240 among 5,842

inmates of the Hong Kong Prison. The possibility exists of significant regional differences in the frequency of this defect in the Orient.

From the standpoint of comparative teratology—and to establish the basis for certain considerations to be presented in the discussion—it is desirable at this juncture to emphasize two points. 1) The total frequency of major congenital defect as diagnosed by simple physical examination is quite similar in Caucasian and Japanese populations; Negro populations may exhibit somewhat fewer malformations although this point is by no means well established and, further, rests on data derived largely from the (hybrid) American Negro, in whom the (genetic) system responsible for these malformations (see below) may have been disturbed. 2) On the other hand, when one shifts to a detailed comparison of Japanese and Caucasian series in terms of specific malformations, many significant differences become apparent, i.e., for four of the six defects selected for comparison. It must be emphasized again that the basis of selection for this comparison was solely the ease and certainty of diagnosis.

III. THE PATTERN OF CONGENITAL MALFORMATIONS IN MULTIPLE BIRTHS AS REVEALED BY CLINICAL EXAMINATION SHORTLY AFTER BIRTH

The lower frequency of multiple births among Japanese as compared with Caucasians, due to a relative deficiency of dizygotic twins, was first pointed out by Komai and Fukuoka (literature review in Komai, 1937; see also Inouye, 1957). The present material confirms these earlier observations, the frequency of multiple births in the three cities under study being, for non-consanguineous parents, 1 in 163 births during the period 1948–1953, and the ratio of like-sexed pairs to unlike-sexed pairs of 5.51 suggesting a monozygous:dizygous ratio of 2.25.

A total of 773 infants who are the product of multiple births meet the restrictions placed upon the material of the preceding section. City-wise, they are distributed as follows: Hiroshima—269 infants; Nagasaki—412 infants; and Kure—92 infants. The data include only one set of triplets. The major defects encountered on clinical examination, and the findings in the other twin, are shown in Table 6. There are 9 (1.16 per cent) infants with major defects, a frequency in complete agreement with

TABLE 6. CONGENITAL DEFECTS APPARENT TO PHYSICAL EXAMINATION AMONG THE 773 INFANTS IN THIS SERIES RESULTING FROM MULTIPLE BIRTHS. IN NO CASE WERE BOTH MEMBERS OF THE TWIN PAIR ABNORMAL. IN COLUMN TWO THE SEX OF THE AFFECTED TWIN, IS ALWAYS GIVEN FIRST

Registration no.	Sex of twins	Defect
H23807	M-M	acardiacus amorphous with atresia ani
H24706	M-M	anencephaly
H32074	F-F	omphalocele
N07777	M-F	hypospadias
N13125	F-F	harelip and cleft palate
N16114	M-M	cystic hygroma
N24892	F-F	atresia ani et vaginae; club foot
K04058	F-M	extreme bilateral underdevelopment of forearm and leg, i.e. partial phocomelia
K06776	M-M	congenital dislocation of left hip

the frequency observed among single births. Two of the 9 twin pairs are of unlike sex. Of the 7 like-sexed pairs, 5 might be expected to be monozygous, and two dizygous, although the sampling error is of course large. It is noteworthy that for none of the like- (or unlike-) sexed pairs is there concordance as to defect. The genetic implications of this will be considered in a subsequent section.

IV. THE AUTOPSY FINDINGS

Early in the study of the potential genetic effects of the atomic bombs, an attempt was initiated to conduct autopsy examinations on as many infants who were stillborn or died during the neonatal period as possible. The details of this program have been given elsewhere (Neel and Schull, 1956). For a variety of reasons, the autopsy program in Nagasaki was subject to biases which render its use for normative purposes hazardous. On the other hand, in Hiroshima, between May of 1949 and the termination of the program in 1954, some 62.8 per cent of all infants who were stillborn or died during the neonatal period came to autopsy, and these are thought to constitute a representative series. Among the 26,281 Hiroshima children, both single and multiple births, who are the subject of this report, there were 310 who between the above-mentioned dates were stillborn or died during the neonatal period, who meet the restrictions placed on this series, and who were autopsied. The findings in these children are given in a series of four tables. Table 7 summarizes the extent to which the autopsy series revealed major defect not apparent on clinical examination, while Tables 8, 9, and 10 describe the detailed autopsy findings. These latter tables appear to summarize one of the first extensive autopsy series on material of this type from Japan.

It will be noted that among the 264 children who went to autopsy without the clinical diagnosis of major defect, 27 or 10.2 per cent were found to have major internal defects. Among the 26,281 children (single and multiple births) who comprise the Hiroshima series, there were a total of 774 normal appearing children who were stillborn or died during the neonatal period. Among the 30,652 children comprising the Nagasaki series, the comparable figure is 981, while for Kure, the number is 233. The total number of normal appearing children who were stillborn or died during the neonatal period in these three cities is thus 1,988. Applying the 10.2 per cent figure for major defect derived above, some 203 of these children should have had one or more major defects. This number, added to the 660 already known,

TABLE 7. THE CONTRIBUTION OF THE AUTOPSY PROGRAM TO THE DELINEATION OF THE CONGENITAL DEFECTS OCCURRING AMONG BIRTHS IN HIROSHIMA

Findings on the basis of clinical examination and autopsy	Number
Children with no major defect on clinical examination and none found at autopsy	237
Children with no major defect on clinical examination but major defect found at autopsy	27
Children with major clinical defect on clinical examination, no additional defect diagnosed at autopsy	25
Children with major clinical defect, with either significant modification of clinical impression at autopsy or discovery of additional major defect	21
	310

TABLE 8. A LISTING OF THE ANATOMICAL FINDINGS ENCOUNTERED IN THE 27 CHILDREN FOUND TO HAVE MAJOR DEFECT OUT OF A TOTAL OF 264 CHILDREN WHO WERE STILLBORN OR DIED DURING THE NEONATAL PERIOD, WHO CAME TO AUTOPSY, AND WHO AT THE TIME OF AUTOPSY WERE NOT KNOWN TO HAVE A MAJOR CONGENITAL DEFECT

Type of Malformation	Number
Musculoskeletal	
defect of left leaf of diaphragm with herniation of abdominal organs into left pleural cavity	4
Respiratory	
tracheo-eosphageal fistula	1
Cardiovascular	
cardiac hypertrophy, cause undetermined	1
interventricular septal defect	6
subaortic stenosis with cardiac hypertrophy and dilatation	1
absence of pulmonary veins with return of pulmonary blood to left innominate vein	1
interventricular septal defect; dextroposition of aorta	1
interventricular septal defect; coarctation of aorta; bicuspid aortic valve	1
Digestive	
incomplete rotation of colon	1
Urogenital	
horseshoe kidney	1
hydronephrosis, bilateral, marked, without determined organic obstruction	1
polycystic disease of kidneys	1
ectopic, hypoplastic left kidney with aplasia of left ureter; ectopic urethral orifice (anterior vaginal wall); uterus bicornis unicollis	1
Complex, multi-systemic	
tracheo-esophageal fistula; interventricular septal defect; anomalous lobation of lungs	1
stenosis of ascending aorta and hypertrophy of proximal pulmonary artery, with right ventricular hypertrophy and dilatation; rotation of stomach to right; right-sided spleen	1
absence of proximal portion of pulmonary artery, left-sided aorta, interventricular septal defect, and rotation of heart to right; absence of spleen	1
interventricular septal defect; atresia of small intestine	1
bilateral renal and ureteral aplasia, hypoplasia of bladder, persistence of urachus; internal hydrocephalus	1
fused kidneys, lying on right, absence of left fallopian tube; single lobed left lung	1
Total defective children	27

would raise the total figure for major defect to 863, or 1.3 per cent of the 64,569 single and multiple births in the three cities. While this figure will be used in calculating the total frequency of major congenital defects in Japanese births, it must be emphasized that it is only to be regarded as an approximation.

A number of the available series on the frequency of congenital defect in Caucasian infants are obviously based on a mixture of physical examination and autopsy findings, but the proportion of infants upon whom a postmortem examination was performed is not clearly stated. These series also usually include defects which in the present study would be considered minor. As a very rough basis for comparison

TABLE 9. A LISTING OF THE ANATOMICAL FINDINGS IN 25 INFANTS KNOWN AT THE TIME OF AUTOPSY TO HAVE MAJOR DEFECT, IN WHOM THERE WERE NO ADDITIONAL FINDINGS AT AUTOPSY

Type of Malformation	Number
Musculoskeletal	
club foot	2
club foot; oligodactyly of right upper extremity	1
Digestive	
atresia ani	1
gastroschisis	1
omphalocele	2
harelip and cleft palate	3
Nervous	
anencephaly	9
Complex	
achondroplasia	1
harelip and cleft palate; club feet	2
occipital meningoencephalocele; fissure of right ear	1
occipital meningoencephalocele; syndactyly of right foot; shortening of right forearm with hypoplasia of right digits	1
acardiacus amorphous	1
Total defective children	25

with the above-mentioned figures, the following findings in Caucasian infants may be mentioned: Lucy (1949)—1.8 per cent of 11,881 (U.S.A.), Stevenson, Worcester, and Rice (1950)—1.7 per cent (minimum) of 29,024 (U.S.A.), Carter (1950)—1.4 per cent of 14,813 (England), Böök (1951)—1.3 per cent of 44,109 (Sweden). These figures are not strictly comparable with the Japanese figure given above, since the latter is an extrapolation based on a known proportion of autopsies, whereas the other figures are based on a considerable (but unstated) proportion of autopsies.

V. THE FINDINGS IN CHILDREN BORN OF CONSANGUINEOUS PARENTS

Schull (1958) has presented the findings with respect to congenital malformations in a group of Japanese children meeting the restrictions placed upon this series except for the fact that they were born to consanguineous parents. Among 4,845 such children, there were 69, or 1.42 per cent, found to have major defects in the course of a standard pediatric examination at or shortly following birth. This group also includes 160 children who were stillborn or died during the neonatal period, without signs on clinical examination of major defect. Assuming that the proportion of children with gross defect detectable at autopsy is the same for this group as for the corresponding children of non-consanguineous parents (10.2 per cent; probably an underestimate), then one would anticipate some 16 grossly malformed children among this group, or a total of 85 such children among the 4,845 born to consanguineous parents. Combining these figures with those previously derived, the total number of children with one or more major congenital defects among a group of 69,414 Japanese births selected at random and studied at or shortly after birth by these methods becomes 948, or 1.37 per cent.

TABLE 10. A LISTING OF 21 INFANTS KNOWN TO HAVE MAJOR DEFECT AT THE TIME OF AUTOPSY, IN WHOM THE POST-MORTEM EXAMINATION EITHER PROVIDED ADDITIONAL DIAGNOSES OF MAJOR DEFECT OR RESULTED IN A REVISION OF THE ORIGINAL DIAGNOSIS. BECAUSE OF THE FACT THAT THE DIAGNOSES IN ALMOST ALL CASES INVOLVE MULTIPLE SYSTEMS, THE LISTING IS SIMPLY ALPHABETICAL ON THE BASIS OF THE APPARENTLY MOST SERIOUS CLINICAL DIAGNOSIS

Clinical Diagnosis	Autopsy (additional or revised) findings
Absence of mandible; cleft palate; hypoplastic tongue	complete situs inversus viscerum; agenesis of right kidney and ureter
Anencephaly	harelip
Anencephaly	left polycystic kidney
Anencephaly	infundibular stenosis of heart
Anencephaly	stricture, right kidney
Anencephaly; cleft palate	omental cyst
Anencephaly; cleft lip and palate	complex defect, great vessels of heart
Anencephaly; harelip and cleft palate; polydactyly	polycystic liver and kidneys; interventricular septal defect
Anophthalmos, bilateral	hamartoma of skin of neck, bilateral; absence of internal ears; atresia of aorta with hypertrophy of proximal pulmonary artery, absence of distal pulmonary artery and veins, interauricular and interventricular septal defect, absence of mitral valve; absence of trachea, bronchi, and lungs; left diaphragmatic hernia.
Atresia ani, oligodactyly	tracheo-esophageal fistula
Cleft palate	incomplete rotation of large intestine
Dextrocardia	defect of left leaf of diaphragm with herniation of abdominal organs into left pleural cavity
Harelip and cleft palate	hypoplasia of aorta, interventricular septal defect
Harelip and cleft palate	interauricular and interventricular septal defect
Harelip and cleft palate; bilateral malformation of toe (incipient polydactyly)	interventricular septal defect; bicornuate uterus and duplex vagina
Hydrocephalus	teratoma in brain
Microphthalmos, right	aplasia of lungs, pulmonary arteries and veins, with atresia of trachea
Omphalocele; polydactyly right hand	defect of pericardium and diaphragm
Spina bifida with bilateral club foot; rudimentary external ears with absence of external auditory canal; hypoplasia of external genitalia	interventricular septal defect
Sympodia; atresia ani; absence of genitalia	absence of genitourinary system
Tumor, type undetermined	sacral teratoma

VI. THE RESULTS OF A RE-EXAMINATION AT AGE NINE MONTHS

One feature of the Genetic Program of the ABCC was an attempt, initiated in January of 1950, to re-examine, during the latter part of the first year of life, as many of the liveborn infants registered with the Program as possible, the limiting factor in the number examined being the clinical facilities available. Infants were scheduled for re-examination in a random fashion, according to the terminal digit

TABLE 11. A LISTING OF CHILDREN IN WHOM MAJOR DEFECT WAS DETECTED SHORTLY AFTER BIRTH, WHO WERE RE-EXAMINED AT AGE 8 TO 10 MONTHS AND NO ADDITIONAL MAJOR DEFECT NOTED

Defect	Number
Musculoskeletal	
arthrogryposis multiplex congenita	1
brachydactyly	1
brachydactyly with syndactyly	1
club foot	5
dislocation of hip	3
inguinal hernia	4
maldevelopment right hand with syndactyly	1
oligodactyly	2
oligodactyly and syndactyly; absence right tibia and astragalus	1
polydactyly	5
polydactyly and syndactyly	2
syndactyly	1
Cardiovascular	
congenital heart disease, type undetermined	26
Hemic and lymphatic	
cystic hygroma	3
Digestive	
harelip	10
harelip and cleft palate	12
cleft palate	4
Organs of special sense: eye	
anophthalmos	1
anophthalmos-microphthalmos; coloboma iridis	1
leukoma of cornea	1
Organs of special sense: ear	
microtia	3
microtia with auricular appendages	1
malformation of ear	3
Multiple or complex	
complex and ill defined	1
cleft palate; acetabular dysplasia	1
congenital heart disease, type undetermined; polydactyly	1
mongolism	1
mongolism, syndactyly	1
Total defective children	97

in their genetics registration number. An attempt was made to schedule the examination at age 9 months, but some infants were seen at age 8 or 10 months. No infant seen before the age of 8 months or after the age of 10 months is included in this series. Infants born in the city of Kure were not included in this follow-up program.

From the 57,025 Hiroshima-Nagasaki infants who meet the restrictions of this study, 16,144 infants were subjected to this follow-up examination (cf. Table 8.14, Neel and Schull, 1956). The physical examinations were carried out by Japanese and American pediatricians who had at their disposal the usual X-ray and laboratory facilities. The findings are presented in three tables. The first of these (Table 11) lists infants known to have major defect at the time they were re-examined, on

TABLE 12. A LISTING OF CHILDREN (a) IN WHOM MAJOR DEFECT WAS DIAGNOSED SHORTLY AFTER BIRTH, WHO WERE RE-EXAMINED AT AGE 8 TO 10 MONTHS AND ADDITIONAL MAJOR DEFECT FOUND, OR (b) IN WHOM A MAJOR DEFECT WAS DIAGNOSED SHORTLY AFTER BIRTH, BUT THIS WAS NOT VERIFIED AT THE 8 TO 10 MONTHS EXAMINATION, ALTHOUGH OTHER MAJOR DEFECT WAS PRESENT

a. Original defect	Added defect
club foot	acetabular dysplasia
club foot	mental deficiency
club foot	pilonidal sinus
hypospadias	pilonidal sinus
inguinal hernia	funnel chest
microcephaly	mental deficiency
polydactyly	congenital heart disease, type undetermined
polydactyly	congenital heart disease, type undetermined
polydactyly	malformation of ear
spina bifida with myelomeningocele	hydrocephalus, mental deficiency
syndactyly	brachydactyly
b. Original (unconfirmed) defect	**New defect**
club foot	acetabular dysplasia; mongolism
congenital heart disease, type undetermined	disease of cornea
club foot	microphthalmos*

* Recognized at birth, but through clerical error not listed as a diagnosis.

the basis of the earlier examination, in whom there were no additional findings. Table 12 lists infants known to be defective, on whom there *were* additional findings. Finally, Table 13 lists infants in whom defect was first detected in connection with this "9-months" examination. Only these latter infants increase the number (and proportion) of defective children in the total sample. The sum of these three tables will not, of course, represent the total amount of congenital defect occurring in a population of this nature, since many children with congenital defect will have died prior to age nine months. However, if one adds the percentage of defect given in Table 13 (1.75 per cent) to the percentage derived earlier (1.37 per cent), the sum (3.12 per cent) will correspond to the total amount of defect detectable by the approaches employed in this study.

There is known to the author only one series ***roughly*** comparable to the present, that compiled by McIntosh et al. (1954). Before contrasting our findings with those of these investigators, attention should be again directed at the arbitrary nature of any listing of major congenital defect. We have attempted in the present series to use the term as indicating defect posing an actual or potential health problem of some importance. This has led to disregarding such relatively common variations as preauricular pits, deformity of the uvula, hydroceles at birth, skin papillomas and nevi, and supernumerary nipples. We have also disregarded—and this will be questioned by some—umbilical hernias in both sexes, and inguinal hernias in males.

McIntosh et al. (1954) report a total of 7.5 per cent of children with congenital defect in a sample of 5,530, of which 3,101 were listed as white and 2,429 as non-white, the latter largely American Negro. On the face of it, this is over twice the amount of defect encountered in this series. However, from the listing of types of malformations given in their paper, it is apparent they have included in their series types of defects excluded in the present study. The corrections which would

TABLE 13. A LISTING OF CHILDREN IN WHOM NO MAJOR DEFECT WAS OBSERVED AT THE EXAMINATION SHORTLY AFTER BIRTH, BUT IN WHOM ONE OR MORE MAJOR DEFECTS WERE OBSERVED AT AN EXAMINATION PERFORMED WHEN THEY WERE 8–10 MONTHS OF AGE

Defect	Number
Musculoskeletal	
club foot	3
congenital contracture of ligaments to toes, bilateral	1
dislocation of hip	106
funnel chest	7
hypertelorism	1
inguinal hernia (♀ ♀ only)	32
microcephaly (mental deficiency)	5
microdactyly, third toe, bilateral	1
micrognathia	1
polydactyly	1
syndactyly	1
underdeveloped (short) right leg, cause unknown	1
Respiratory	
congenital stridor	1
Cardiovascular	
congenital heart disease, type undetermined	39
Hemic and lymphatic	
lymphangioma	1
Digestive	
branchial cyst	1
cleft palate	2
hereditary amelogenesis imperfecta	1
thyroglossal cyst	1
Urogenital	
cryptorchism	1
Wilm's tumor	1
Nervous	
cerebral spastic infantile paralysis	3
hydrocephalus	2
mental deficiency (severe)	12
Organs of special sense: eye	
blepharophimosis	1
cataracts (congenital)	1
coloboma iridis	1
corneal opacity (congenital) with nystagmus	1
nystagmus (congenital)	1
nystagmus (congenital) with strabismus	1
ptosis	1
strabismus (severe)	3
Organs of special sense: ear	
microtia	1
Integumentary	
congenital ectodermal defect of scalp	1
ichthyosis	1
Multiple or complex	
achondroplasia	2
atresia ani with rectovaginal fistula; dextrocardia	1
cleft palate; strabismus (severe)	1
congenital heart disease; mental deficiency	1

TABLE 13—*Continued*

Defect	Number
congenital heart disease; strabismus (severe)	1
congenital heart disease; supernumerary breast	2
dislocation of hip; club foot	1
dislocation of hip; diastasis of rectus abdominis	1
dislocation of hip; leukoderma	2
dislocation of hip; torticollis	1
lumbar tumor, hirsute, with spina bifida occulta	1
mental deficiency; dislocation of hip	1
mongolism	11
mongolism; club foot	1
physical retardation, marked, cause unknown	1
situs inversus viscerum	1
Total defective children	267

render the two series comparable cannot be made from the paper of McIntosh et al. (1954) because of the manner in which the data are presented, but through the courtesy of Dr. McIntosh and Dr. Mellin I have received a complete listing of the defective children encountered in their study. Any detailed comparison of the two series is impossible because of differences in the age at which the children were examined, differences in the extent to which X-rays were employed as a routine diagnostic measure, differences in diagnostic standards, etc. After the elimination of defects which would certainly or very probably not have been scored in the present series, the percentage of defective children was approximately 5 per cent. A more meaningful comparison involves the six "objective" defects listed in Table 2. The total frequency of these six defects in the McIntosh series is 1.23 per cent, more than twice the level encountered in this study as well as in any of the other studies listed in Table 2 except that of Malpas (1937). However, this figure is greatly influenced by the high frequency of polydactylism in the Negro which we have already commented on. When this diagnosis is eliminated, the total frequency drops to 0.74 per cent, a figure still in excess of our own and most other studies. There is, then, the likelihood that major congenital defects are more common in the material of McIntosh et al. than in the material of this series or, for that matter, most published series on Caucasian births.

It should be emphasized that neither the figures of McIntosh et al. (1954) nor those presented in this paper represent the total impact of congenital defect upon a population. Thus, it has been recognized for many years (cf. esp. Mall, 1917) that in the neighborhood of 20–25 per cent of early (first trimester) abortuses exhibit major defects. The data on this point have not been assembled in such a fashion that it seems possible to utilize them for normative purposes. Nevertheless, it seems on the conservative side to estimate that at least 5 per cent of all conceptuses are destined to develop *major* congenital defect. The conservative nature of this estimate is particularly evident when it is considered that some serious congenital defects, as of the urogenital system, may not become apparent until the second, third, or even later decades of life. The finding of Hertig and Rock (1949), that out of 28 very early conceptuses recovered in a group of 136 potentially pregnant

women of known fertility who underwent hysterectomy for a variety of therapeutic reasons, 12 appeared abnormal, probably indicates an upper limit for the "malformation load," although at this early stage many major defects would not yet be detectable.

In an earlier section of this paper, the frequency of six specific congenital defects was contrasted for Japanese and Caucasian populations. With the additional material now at hand, a great many more comparisons become possible. However, after a survey of the literature regarding such defects as congenital dislocation of the hip, inguinal hernia, and hypospadias, it has become obvious that many of the comparisons would be misleading, because of differences in diagnostic standards and modes of ascertainment. Furthermore, what is in many ways the most interesting portion of this material, that pertaining to complex or multiple malformations, cannot be compared with that of other series because of the abbreviated ways in which the latter have been presented.

VII. RECURRENCE RISKS

The Genetics Long Form which was routinely completed for each infant with a major congenital defect included provision for a family history, with particular reference to the occurrence of the same or other major defect in the siblings and parents of the propositus. A preliminary tabulation of the results of these histories, in 1952, suggested that the recurrence risks in this population were less than risks which had been reported for various Caucasian populations. The first question to be considered in connection with this apparent finding was the validity of the histories. The birth of a malformed child stigmatizes the family involved, to a greater extent in Japan than in most Western cultures, and it seemed quite possible that the physician-interviewer had not established sufficient rapport with the family to obtain an accurate history. An added factor could be an understandable reluctance on the part of the informant (usually the mother) to disclose the occurrence of a malformation in a stillborn child, if this had not been declared previously. Accordingly, in 1954 an attempt was made by a team of physician-interviewers to revisit the parents of all children with any of the six defects listed in Table 2, as well as for certain other, less common, defects. At this time a repeat history was obtained, after a detailed attempt to explain the scientific uses to which such a history would be put. In addition, as many surviving children as possible were examined. Finally, with respect to the accuracy of the histories obtained, it might be noted that during the six-year period between 1948 and 1954, most of the children born to the informants had actually been examined by ABCC physicians.

The recurrence risks so obtained are listed in Table 14. Several preliminary points should be noted before a detailed consideration of the table is undertaken. The material in the table is subject to the same restrictions regarding radiation exposure history, consanguinity, etc., as the material on which Table 1 is based. However, for a variety of reasons, and principally the movement of the family concerned from the city, it was not possible to revisit the parents of all the children with congenital defects listed in Table 1. One-child families have been omitted from the

tabulation, since they contribute no information. These facts account for the failure of Table 14 to balance with Tables 1 and 2. Concerning the accuracy of the histories obtained from those who were located, one important index is supplied by the history obtained of other major defects apart from the specific defect under investigation, in the siblings of the propositus. A total of four such defects, as well as a "deaf-mute" child, was reported. This frequency, 0.65 per cent, does not differ significantly from the 1.02 per cent of Table 1. On the other hand, the difference is in the direction to suggest underreporting, perhaps purposive, perhaps due to a lack of familiarity with, or diagnosis of, defects occurring in stillborn children.

We may now consider the specific malformations studied with respect to recurrence risks, with a comparison with figures for Caucasian populations. Some of the better known risk figures for the latter are summarized in Table 15. In passing, it should be noted that there is the same paucity of empirical risk figures for the specific malformations under consideration, despite their widespread occurrence in Caucasian populations, as there is for completely reported series of major congenital malformations. For many extensive studies on specific defects (e.g., Sanders, 1934; Polman, 1951), the data have simply not been presented in a form compatible with the derivation of empiric risk figures. In the strict sense, empiric risk figures should deal only with children born after the (affected) propositus. However, among those series which can be used for purposes of comparison with the present data, some fail to make this distinction. Moreover, in the present material, because of the way the data were collected, the number born after the propositus is relatively small. Accordingly, in the comparisons no distinction has been made between children born before or after the propositus, although, for those interested in this point, the distinction has been recognized in Table 14.

On the basis of the material of Tables 14 and 15, three questions can now be briefly considered: 1) In this material, are sibships in which a malformed child has been born subject to an increased risk of malformations of all types? 2) Is there a significant tendency for specific malformations to recur in certain families? 3) How does this tendency, if any, compare with similar figures for Caucasian populations? Attempts to answer these questions are handicapped by the relative paucity of material with respect to any specific malformation. This same paucity of material renders any precise statistical analysis of dubious value. Because of the findings of Fogh-Andersen (1943), suggesting that isolated cleft palate should be regarded as etiologically distinct from harelip with or without an associated cleft palate, the two conditions have been treated as separate entities.

The question of an increased risk of malformations of all types (exclusive of the specific defect which brings the family to attention) has already been touched upon. The limited data supply no evidence that this is the case. With respect to Caucasian populations, the data of Murphy (1947) appear to show that in addition to an increased recurrence risk for the same defect present in the propositus, there is also an increased susceptibility in subsequent children to malformations of other types. Although the manner in which the data are presented precludes an exact statement, with respect to Murphy's study this increase was perhaps two- to four-

TABLE 14. RECURRENCE RISKS WITH RESPECT TO SEVEN CONGENITAL DEFECTS ENCOUNTERED IN HIROSHIMA AND NAGASAKI. THE "E" IN THE NEXT TO LAST COLUMN DENOTES THE EXPECTED NUMBER OF RECURRENCES ON THE BASIS OF CHANCE. ALL FAMILIES WERE ASCERTAINED ONLY ONCE

Trait	No. of propositi	No. of children born before propositus	No. with same defect	No. with other major defect	No. of children born after propositus	No. with same defect	No. with other major defect	Total no. of children (excluding propositus)	No. with same defect	No. with other major defect
Anencephalus										
simple	29	58	0	0	22	0	1 (harelip, cleft palate)	80	0	1
complicated	5	4	0	0	2	0	0	6	0	0
Total	34	62	0	0	24	0	1	86	0 E = 0.056	1
Spina bifida										
simple	7	19	0	0	7	0	0	26	0	0
complicated	2	3	0	0	0	0	0	3	0	0
Total	9	22	0	0	7	0	0	29	0 E = 0.006	0
Anophthalmos-microphthalmos										
simple	9	14	0	0	4	1	0	18	1	0
complicated	2	5	0	0	0	0	0	5	0	0
Total	11	19	0	0	4	1	0	23	1(4.35%) E = 0 006	0

Atresia ani										
simple	4	12	0	0	1	0	0	13	0	0
complicated	11	30	0	1 (harelip, cleft palate)	9	0	0	39	0	1
Total	15	42	0	1	10	0	0	52	0 E = 0.015	1
Harelip ± cleft palate										
simple	76	167	4	2[1]	28	0	0	195	4	2
complicated	14	43	0	0	3	0	0	46	0	0
Total	90	210	4	2	31	0	0	241	4(1.66%) E = 0.63[4]	2
Cleft palate alone										
simple	19	53	1 + 1 + 2?[2]	0	6	0	0	59	1 + 1 + 2?	0
complicated	4	12	0	0	1	0	0	13	0	0
Total	23	65	2 + 2?	0	7	0	0	72	2 + 2? (5.56%) E = 0.019[4]	0
Polydactyly										
simple	33	73	1	1[3]	9	0	0	82	1	1
complicated	11	30	0	0	3	0	0	33	0	0
Total	44	103	1	1	12	0	0	115	1(0.87%) E = 0.107	1
Grand total	226	523	7 + 2?	4	95	1	1	618	7 + 1 + 2?	5

[1] Stillbirth alleged to have "tumor" of right shoulder region; other child with atresia ani.

[2] The two questionable recurrences lack medical confirmation; children now deceased. One of the positive recurrences is actually a child with harelip.

[3] Child alleged to be deaf mute.

[4] "E" calculated for recurrence of either harelip with or without cleft palate *or* isolated cleft palate.

TABLE 15. EMPIRIC RISK FIGURES FOR FOUR COMMON CONGENITAL DEFECTS IN CAUCASIAN POPULATIONS

Defect	Investigator	Number of siblings of propositi	Number with same defect	Risk	Number with other major defect
Anencephalus	Böök & Rayner, 1950	88	0		1 spina bifida
					0 other defect
	Record & McKeown, 1950	582	3		2 spina bifida
					1 hydrocephalus
					0 other defect
	Penrose, 1946	48	2		2 spina bifida
					3 other defect
		718	5	0.70	
Spina bifida	Record & McKeown, 1950	654	10		7 anencephalus
					1 hydrocephalus
					0 other defect
	Penrose, 1946	249	8		2 anencephalus
					20 other defect
	Hindse-Nielsen, 1938	548	28		?
		1451	46	3.17	
Harelip ± cleft plate	Fogh-Andersen, 1943	1081	40		?
	Fraser & Baxter, 1954	140	9		?
		1221	49	4.01	
Isolated cleft palate	Fogh-Andersen, 1943	493	9		?
	Fraser & Baxter, 1954	101	3		?
		594	12	2.02	

fold. Other studies have not shown a non-specific risk of this magnitude, and, in fact, suggest no particular increased risk for malformations in general among the sibs of propositi (Record and McKeown, 1950).

With respect to the second question, of specific recurrence risks, it may be pointed out that whereas because of the small numbers involved, the mean number of recurrences expected for any specific defect on the basis of chance is below, and usually well below, 1.0, for each of the seven defects considered, nevertheless in four cases one or more recurrences was noted. On the "specific recurrence" hypothesis the total number of recurrences expected is 0.839, whereas the observed number is between 7 and 10, undoubtedly a significant difference although no precise statistical evaluation suggests itself. The indecision as to whether the precise recurrence figure is 7 or 10 springs from the findings regarding isolated cleft palate. Two re-reported recurrences lack medical verification, and another is a case of harelip. It seems more than coincidence that this occurred in a sibship which also contained a child with cleft palate, and we have scored it as a recurrence, but were it desired to consider it as "other major defect," the picture would of course not be materially changed.

We come now to the question of how these empiric risk figures compare with

those derived from Caucasian populations. Again, the smallness of the numbers involved vitiates any detailed comparisons. For only four of the defects listed in Table 14 (anencephalus, spina bifida, harelip and/or cleft palate, isolated cleft palate) has it been possible to locate satisfactory empiric risk figures. These are summarized in Table 15. On the face of it, the Japanese figures are below the Caucasian in three out of the four comparisons, although the tenuous nature of the comparison is underlined by the fact that even a single recurrence with respect to anencephalus or spina bifida would have resulted in the Japanese risk figures exceeding the Caucasian.

The etiological inter-relatedness of anencephalus and spina bifida and especially the tendency of the two defects to occur in the same sibship, has been stressed by a number of investigators (e.g., Penrose, 1946; Record and McKeown, 1950; MacMahon, Pugh, and Ingalls, 1953). The present very scanty data fail to bear this out, but the numbers are too small to be very meaningful. Böök and Rayner (1950) have emphasized the high abortion rate in sibships in which anencephalics occur. In the present data, in addition to the 85 term or near-term siblings of anencephalics listed in Table 13, there were 6 spontaneous abortions, or 6.6 per cent of the reported pregnancies. For all the remaining defects, in addition to the 532 term or near-term siblings, there were 43 spontaneous abortions reported, or 8.1 per cent. The data therefore fail to support the finding of Böök and Rayner.

No empiric risk figures for atresia ani have come to light. Neither do there appear to be such figures for polydactyly. However, a voluminous literature attests to the tendency of this latter trait in Caucasian and Negro populations to affect multiple members of a kindred, most often in a pattern suggesting dominant inheritance but sometimes more suggestive of recessive heredity (literature summaries in Bauer and Bode, 1940; Gates, 1946), and the "self-evident" genetic nature of the trait has perhaps discouraged the accumulation of empiric risk figures. It is difficult to judge how representative a picture of the overall situation the literature provides. However, on the face of it only 1 recurrence in 115 sibs of affected individuals in the Japanese data is quite striking. This impression, of a relative paucity of pedigrees illustrating simple modes of inheritance for polydactyly, is borne out by the Japanese literature (summaries in Komai, 1934, 1947; Ohkura, 1956).

There appear to be no empiric risk figures for microphthalmos-anophthalmos in Caucasian populations, presumably because of the rarity of the trait. There is, however, the extensive study of Sjögren and Larsson (1949) on this condition in Sweden. These investigators distinguished between microphthalmos-anophthalmos with oligophrenia, and the same defect without coincident oligophrenia. With respect to the former, because of the absence of affected parents, an increased consanguinity rate among the parents, the occurrence of multiple cases in some sibships, and the manner of relationship when several sibships within a kindred contain affected individuals, it is concluded that "the only uniform mode of inheritance that is plausible . . . is a partially sex-linked recessive mode with a reduced degree of manifestation." The possibility of genetic heterogeneity is recognized. With respect to microphthalmos-anophthalmos without oligophrenia, because of the occurrence of parent-child combinations, the fact that where neither parent is affected only isolated cases are encountered in a sibship, and the absence of an increased consanguinity rate

among the parents of affected children, it is concluded that dominant inheritance with relatively frequent mutation is the rule. Our own data do not permit a breakdown into these two types, since the children were not followed long enough for a decision regarding the presence of oligophrenia. By combining their observations on the two defects, utilizing only sibships with unaffected parents, not secondarily ascertained, and scoring each sibship as many times as it contains affected individuals, we may obtain a figure to compare with the empirical risk figure of this series. It should be recognized, however, that if there are in fact several different entities involved, whose representation might differ in the two series, then the comparison might be misleading, and at the least must be made with reservations. The total recurrence risk in the series of Sjögren and Larsson may be put at 12 out of 388 siblings, or 3.09 per cent, a figure not differing from the Japanese experience.

In summary, then, the present rather scanty material suggests significantly increased, malformation-specific recurrence risks but is, with one possible exception, not sufficient to establish whether recurrence risks in Japanese material differ from those in Caucasian. The one possible exception appears to be polydactyly, where the risk appears to be lower in Japanese populations.

VIII. THE ASSOCIATION OF MAJOR DEFECTS

The fact that more children exhibit multiple major defects than would be expected on the basis of the individual frequencies of these defects has been noted by many investigators, and emerges again in this study. Given the frequencies noted in the Japanese population for various specific defects, a disproportionate number of infants exhibit two or more of these defects. By way of an example, Table 16 presents the findings with respect to the association of other defects with the three principal congenital defects of the central nervous system in the material of this series. As a basis for comparison with the findings in Caucasian infants, the extensive study of Record and McKeown (1949) has been utilized. A difficulty which arises in the comparison is that while it is apparent from the nature of the listing that autopsy findings contribute to some extent to the "coexisting deformities" observed by Record and McKeown, it is not clear how the per cent of autopsies performed in their series compares with the per cent in this series. Accordingly, in this comparison no autopsy diagnoses have been included for the Japanese material. Two points emerge from a consideration of these two sets of data. Firstly, even excluding all autopsy diagnoses for the Japanese material the tendency for an individual with one of these central nervous system malformations to exhibit one or more other major defects appears to be greater in the Japanese than in the Caucasian series ($\chi^2 = 19.72$, d.f. $= 1$, $P < .001$). Inspection of Table 10 serves to indicate how much greater the difference would be if autopsy diagnoses were included. Secondly, we may consider the question of what relationship this association bears to the pattern of malformation in the entire population. Here we are handicapped by the relatively small numbers involved, and also by the fact that in the Caucasian series there appear two rather cryptic entries, namely "other malformations" and "multiple malformations." Professor McKeown has kindly made available a listing for the "other malformations," but a similar listing is not available for the "multiples" (cf. the first footnote, Table 16). For analytic purposes, the latter situation can be met by certain arbitrary assumptions. Two

TABLE 16. A COMPARISON OF THE MALFORMATIONS ASSOCIATED WITH ANENCEPHALUS, SPINA BIFIDA, AND HYDROCEPHALUS, IN CAUCASIAN AND JAPANESE BIRTHS, FROM THE DATA OF RECORD AND MCKEOWN (1949) AND THIS PAPER. CLUB FOOT HAS BEEN EXCLUDED AS AN "ASSOCIATED DEFECT" BECAUSE OF THE FACT THAT IN MOST INSTANCES IT IS ONLY ANOTHER MANIFESTATION OF THE NERVOUS SYSTEM MALFORMATION

Coexisting Deformity	Type of Central Nervous System Malformation: Anencephaly (± spina bifida)	Spina bifida (± hydrocephaly)	Hydrocephaly	Total
a. Caucasian (Record & McKeown, 1949)				
Exomphalos	9	2	—	11
Congenital heart	—	2	3	5
Harelip and/or cleft palate	—	3	—	3
Malformation of cord	1	1	—	2
Other skeletal deformities	2	8	4	14
Other malformations	1	2	2	5
Multiple malformations	1	—	5	6[1]
Total number of deformities	14	18	14	46
Number of individuals exhibiting these[2]	13	16	41	43
Total number in group	366	389	150	905
Percentage of individuals with co-existing deformity	3.6	4.1	9.3	4.75
b. Japanese (this series)				
Anophthalmos	1	—	—	1
Harelip and/or cleft palate	2	—	1[3]	3
Microtia	—	—	1	1
Tumor, hand, ?type	1	—	—	1
Malformation of ears	—	—	1	1
Multiple malformations:				
harelip and cleft palate; arhinia	—	—	1	1
harelip and cleft palate; omphalocele; club foot	1	—	—	1
harelip and cleft palate; polydactyly	1	—	—	1
malformation of ears; probably hypospadias	—	1	—	1
cleft palate, absence of right radius and thumb	—	1	—	1
Total number of deformities	9	4	5	18
Number of individuals exhibiting these	6	2	4	12
Total number in group	40	13	15	68
Percentage of individuals with co-existing deformity	15.0	15.4	26.7	17.6

[1] Prof. McKeown (personal communication) states that "no details of 'multiple malformations' were given in the death records from which the series was assembled and we therefore counted each as a single defect." By contrast, each defect has been enumerated for the Japanese series. This difference in the treatment of the two series should not influence the comparisons as regards harelip and omphalocele.

[2] Estimated from the authors' Table 9.

[3] In this case, the diagnosis of hydrocephaly was borderline, and the child could not be followed to establish the diagnosis because of non-viability.

associated defects occur in the series with a sufficient frequency to permit tentative comparisons. One is harelip and/or cleft palate. In the Japanese material, of 18 associated defects, 7 (38.9 per cent) were harelip and/or cleft palate. In the Caucasian material, if we assume that, as in the Japanese series, approximately half the instances of "multiple malformations" involve, as one aspect of the complex, harelip and/or cleft palate, the frequency is 6 of 46, or 13.0 per cent [χ^2 (corrected for continuity) = 3.86, d.f. = 1, $P < .05$]. In absolute terms, harelip and/or cleft palate appear as an associated defect in the Japanese material in 7 out of 68 cases of these three defects of the central nervous system, wnereas the maximum frequency in the Caucasian material would be 9 in 905 cases. The difference is significant ($\chi^2 = 33.82$, d.f. = 1, $P < .001$). Harelip thus appears to be both absolutely and relatively more commonly encountered as an associated defect in the Japanese material. Inasmuch as there was—embarrassingly—one child with anencephaly whose harelip was first recorded by the pathologist, the difference between the two series would again be greater if autopsy findings were taken into consideration. It will be recalled that harelip and/or cleft palate is significantly more frequent among Japanese than among Caucasians. We will return to the genetic implications of this finding in the discussion.

The second defect which may be associated with these central nervous system malformations which warrants comment is what Record and McKeown have termed exomphalos; this corresponds to the defect that, depending on degree, has been termed omphalocele or gastroschisis in this series. This occurred as an associated defect 11 times in the Caucasian series but only once in the Japanese. It thus appears to be relatively (but not absolutely) more common as an associated defect in the Caucasian series. We have not previously considered the frequency of this defect. The incidence of exomphalos in infants born in Birmingham between the years 1941 and 1951 was 0.00031 (69 cases in 221,041 births) (McKeown, MacMahon and Record, 1953). In the Japanese material, the frequency of omphalocele and gastroschisis combined is 0.00014. Again, then, there is some evidence to suggest that the difference in the two series parallels the population incidence figures.

A second major defect which by way of an example may be treated in the same fashion as has just been done for the associated defects of the central nervous system is atresia ani. Although there are in the literature quite a number of series describing the types of defects which may be associated with atresia ani, these have for the most part been compiled at referral centers, which entails a considerable amount of selection, and also often include an unspecified proportion of autopsy findings. However, tentative comparisons are possible if we restrict the comparison to defects detectable by the usual clinical examination and compatible with life. In the present series, of 15 infants with atresia ani, 8 had one or more associated defects on simple clinical examination, for a total of 11 defects (rectovaginal fistula is not counted as an associated defect). Two of these infants (13.3 per cent) had harelip and/or cleft palate. In the Caucasian series of Moore and Lawrence (1952), which of the various series in the literature seems most nearly like this one, although still biased by the fact that these were surgical referrals, 120 children with anal atresia exhibited 190 associated defects, many diagnosed only at autopsy. Two of the 120 children (1.7 per cent) had harelip and/or cleft palate. Again, then, we note the more frequent occurrence of

harelip and/or cleft palate as a defect associated with another type of major malformation in Japanese births, with their higher overall frequency of harelip and/or cleft palate, than in Caucasian births.

IX. DISCUSSION

The growing relative importance of congenital defects of all types in modern Western medicine is so well known as to require no comment. The present data would seem to establish the fact that a very similar problem will soon exist for Oriental populations as, with a rising standard of living and the extension of public health practices, their disease patterns become more comparable to those of the West.

Certain aspects of the present data, taken in conjunction with what is known of congenital defect in Caucasian populations, are conducive to speculation concerning the biological significance of congenital defect. It is, to begin with, a frequently enunciated truism that from the etiological standpoint, congenital defects are undoubtedly quite heterogeneous (e.g., Penrose, 1951; Neel, 1957; Warkany, 1958). Indeed, even for any single, apparently specific defect, there is undoubtedly a multiplicity of etiological pathways leading to that particular phenotype. Thus, congenital cataract may result from maternal (and fetal) rubella during the early months of pregnancy, or from a specific genetic inheritance. At the moment, viewing congenital defects both individually and collectively, probably something less than 10 per cent can be attributed to single, completely penetrant genes, either dominant or recessive. Likewise, the present evidence does not suggest that more than 10 per cent of all congenital defects can be attributed purely and simply to maternal illness, malnutrition, etc. during pregnancy and their consequences for the fetus. What now, of the etiology of the remaining 80 per cent?

A recapitulation of the salient findings in these data

Any attempt to reach an understanding of the biological significance of congenital malformations must take into consideration the following facts which have emerged from our considerations thus far.

1. The total impact of major congenital defect upon Caucasian, Mongolian (Japanese), and, possibly, Negro populations, appears to be very similar. This impression is admittedly somewhat subjective. It is true that there are certain statistically significant differences between these groups. But in many respects, the similarity in total impact overshadows such differences as do emerge. A possible reason for the probable lower frequency of major fatal defect in (American) Negro infants will be discussed later.

2. On detailed comparison of the types and frequencies of specific malformations, it becomes apparent that despite the similarity in total malformation frequency, there are many significant and even striking differences as regards the frequency of specific malformations.

Facts (1) and (2) lead to the conjecture that despite the many obvious differences between European and American populations, on the one hand, and Japanese, on the other, as regards diet, disease experience, and genetic constitution, there is nevertheless in effect in the two populations a similar mechanism regulating the total impact of congenital defect in the populations, although as regards the details of the

system, differences exist which permit specific malformations to vary significantly in their frequency.

The alternative to accepting the postulate of some similar regulatory mechanism in the two populations is to believe that malformations are due to "accidents" which have the same probability of occurrence in the two populations, these accidents the result of such phenomena as mutation pressure or essentially randomly distributed failures of the complex machinery of development to mesh properly, a large proportion of these environmentally triggered. Since, however, "accidents" are no less subject to a deterministic analysis than planned events, the "accident" hypothesis does not relieve the investigator of the responsibility of attempting to analyse the circumstances which produce both the similarities and the differences.

It is, of course, possible to regard the genetically determined portion of congenital malformation as representing only the extreme of the scale of human variation subject to the action of natural selection, and hence requiring no "special" explanation. To a certain extent, this is undoubtedly true. On the other hand, many congenital defects, with the increased risk of fetal loss which they often confer, are scarcely likely to be subject to natural selection, in the competitive sense in which it is usually envisioned, and the impact of congenital defect on a population is such that the question of whether there is perhaps a more recondite explanation of their frequency must be considered.

If, now, this line of reasoning is accepted, then four further facts immediately present themselves:

3. Congenital malformations are not distributed at random in a population, but exhibit significant tendencies to cluster, *in a type-specific fashion*, in certain sibships. As shown earlier, the recurrence risks are small, but, on the basis of admittedly scanty material, appear to be of the same order of magnitude for Japanese and Caucasian populations.

4. In a very scanty twin material, for none of 7 like-sexed twin pairs ascertained through the occurrence of a member with external major defect, was there concordance as to the occurrence (let alone type) of major defect. Because of the distribution of sexes among twin pairs in this material, approximately 5 of these 7 like-sexed pairs may be presumed to have been monozygous.

5. The frequency of a variety of specific malformations in the United States is, in four out of the six instances examined, intermediate between the frequencies observed in England, on the one hand, and Switzerland and Sweden, on the other.

6. In the Japanese material, consanguineous parents have significantly more defective children than non-consanguineous parents. Although the absolute increase is small (from 1.02% in the controls to 1.69% in the children of first cousin marriages; Schull, 1958), the relative increase is marked. Furthermore, it was with respect to the "complex" or "multiple" malformation group and the rarer single malformations that the increase was most apparent. Consanguinity effects have not been prominent in Caucasian series which include a variety of defects, some investigators finding none (Malpas, 1937), others only a slight effect (Murphy, 1947). Significant consanguinity effects have also not been observed in a number of series restricted to a specific defect. Thus Fogh-Andersen observed no excess of consanguinity anong the parents of

children with harelip and/or cleft palate (Fogh-Andersen, 1943); Penrose (1957) notes similar findings with respect to anencephaly and spina bifida. However, such deviation as Fogh-Andersen observed was in the direction of an excess of consanguineous parents, corresponding to the situation in the present material (Schull, 1958), while the present material likewise fails to show an effect of consanguinity in the case of anencephaly. In passing, the relative dearth of observations on the question of a consanguinity effect in congenital malformations as a group should be noted.

Facts (3), (5), and (6), but not (4), all tend to implicate genetic factors as being to some degree responsible for facts (1) and (2). Facts (3) and (5) are consistent with a variety of genetic hypotheses. Furthermore, both of these facts are also compatible with ascribing malformations to some long maintained, non-genetic somatic deviation in the mother, but, as pointed out elsewhere (Neel, 1957), it scarcely seems reasonable to identify this somatic deviation solely with an increased susceptibility to virus or other infections, since the immunity which develops following most infections might be expected to decrease the likelihood of a repeat in subsequent pregnancies, unless one makes the additional postulate of a constitutional inability to produce antibodies in the normal fashion, a postulate which brings us back to genetic concepts. However, fact (6) not only suggests a genetic etiology for congenital defect, but suggests a recessive type of inheritance, although obviously not of a simple, monogenic nature.

A consideration of whether a significant fraction of human congenital defect is due to the existence of multilocal, homeostatic genetic systems

It must be constantly kept in mind that the genetic phenomena responsible for the observed facts are undoubtedly mixed in nature. Thus, facts (3), (5), and (6) can to a considerable extent be "explained" by a judicious admixture of two simple genetic mechanisms, namely, simple recessive inheritance, and simple irregular dominant inheritance. When, however, the total picture is considered, a somewhat more complex possibility comes to mind, namely, that many congenital malformations of various types find a partial explanation in the existence in man of genetic systems of the type discussed in such penetrating and provocative detail by Lerner (1954; see also Dobzhansky, 1955), the malformations ("phenodeviants") being caused "by the intrinsic properties of multigenic Mendelian inheritance, due to which a certain percentage of individuals of every generation falls below the threshold of the obligate proportion of loci needed in a heterozygous state to ensure normal development." The similarity in malformation frequencies in such diverse populations as Japanese and European thus finds an explanation in the fact that there is a malformation frequency representing the optimum balance between, on the one hand, fetal loss and physical handicap from congenital defect, and, on the other hand, population gain from those very same genes which in certain combinations may sometimes result in congenital defect. The differences between populations as regards the frequencies of specific defects would seem to indicate that within the framework of this optimum figure, different populations have evolved genetic systems differing significantly in their details.

Two subpossibilities must be explored, if the possibility is to be considered that

malformations to some extent are segregants from multilocal systems. One can, on the one hand, regard these systems, whatever their role in the organism, as in large part a function of mutation pressure. This point of view makes no assumptions concerning the role of the postulated loci in the economy of the species. One can, on the other hand, consider the possibility that the loci involved contribute to a balanced polymorphic or homeostatic system, with the inference that the genes are in fact playing an important role in the genetic stability of the species.

It is not the purpose of this paper to suggest that *all* of the congenital defects of unknown etiology may be explained in terms of multilocal genetic systems, homeostatic or otherwise. Undoubtedly other environmental and genetic mechanisms are involved. Among the latter must be mentioned dominant mutation and simple but as yet unidentified recessive inheritance. Dominant genes of poor penetrance must also be considered although these latter, if when "non-penetrant" they have effects actually of value to the organism, may also be fitted into a balanced genetic system. However, it *is* desired to call attention to a heretofore largely neglected hypothesis regarding the etiology of a significant fraction of human congenital malformations.

Fact (4) mentioned above, concerning the occurrence of major defect among twins, constitutes the weakest link in the chain of evidence here advanced, concerning the genetic etiology of a considerable fraction of congenital defect. Essentially similar data have been recorded for Caucasian twins by Record and McKeown (1951). Certainly, fact (4) argues strongly against simple dominant or recessive inheritance. It argues less strongly against attributing congenital defect in part to genes or genetic systems where the threshold of gene expression is influenced by "environmental" variables. However, it would appear that if the argument for a genetic etiology of a large fraction of congenital defect is to be reconciled with these findings, it requires the assumption that the responsible genes, or combinations of genes segregating from complex systems, are quite widespread in human populations, with only a small proportion of the potential phenodeviants finding phenotypic expression. It is to be regretted that the twin material is so limited, both in this series and the literature as a whole; the need for additional data of this type is obvious. We shall return to the implications of the twin data again, when considering the association of congenital defects.

To the extent that balanced homeostatic systems contribute to a significant degree to congenital defect, two important conclusions follow:

1. Just as sickle cell anemia is the price certain populations pay for a genetically desirable trait, resistance to malaria, so a certain fraction of congenital malformations may be the price all populations pay for other genetically desirable traits. The nature of these traits is completely unknown. If malaria is eradicated in a community with a high frequency of the gene responsible for the sickling phenomenon, the heterozygote will lose his selective advantage, and the frequency of sickle cell anemia will decrease. By analogy, one approach to the prevention of congenital defect lies in an attempt to discover the function of the postulated homeostatic systems, through studies of the parents of defective children.

However, this concept of congenital malformations, as in part the "price" of certain genetic systems, carries certain obvious implications regarding therapy. The

frequency of congenital malformations is in part a function of maternal age and parity, in both Caucasian and Japanese populations. The inference to be drawn from this and related phenomena is that a better understanding of maternal-fetal physiology may point the way to at least the partial control of the expression of the genotype. With such control, more children of the "malformation genotype" will be born phenotypically normal, and will reproduce normally. Improvements in the care of infants with congenital defect will also lead to the increased survival and reproductive rates. These developments will of course alter the frequencies of the genes involved, with consequences somewhat difficult to visualize, since the "other end" of these homeostatic systems is unknown. If, however, there are sound genetic reasons for the present frequency of malformations, then in general it would appear that in the process whereby a new equilibrium is established, some effect on population fitness is inevitable.

2. Balanced homeostatic systems are not readily disturbed by increases in mutation rate. Until such time as the importance of such systems in human populations is understood, another uncertainty is added to the hazards besetting calculations concerning the effects of increasing exposure to such mutagenic agents as ionizing radiation.

An examination of other data for consistency with the hypothesis

Morton, Crow, and Muller (1956), utilizing principally the data of Sutter and Tabah (1952, 1953) on the death rates of children from consanguineous marriages in rural France, have by an ingenious approach calculated that whereas the average child from unrelated parents had a probability of about .12 of death between birth and sexual maturity, the average complete homozygote, such as theoretically would result from doubling the gamete genome, would have the equivalent of about two lethal genes. The inbreeding "load" in these data would thus appear to be about 17 times as great as the "random" load. Crow (1958) has demonstrated that in a balanced polymorphic system composed of two alleles, with the heterozygote superior to either homozygote, the contribution of the locus involved to the "random" load is equal to its contribution to the "inbreeding" load, and has therefore concluded, on the basis of the French data, that "inbreeding effects are due largely to 'ordinary' gene loci and not those maintained in polymorphic balance." In view of the contribution of congenital defect to death between birth and sexual maturity, and the inbreeding effect seen in congenital defects in Japan, the question must be considered whether there is a conflict between Crow's conclusions and the present attempt to find a basis for a significant proportion of human congenital defect in balanced homeostatic systems.

It should first be recognized that estimates of the magnitude of the inbreeding load present many difficulties. Thus, although Sutter and Tabah (1952, 1953) find rather marked differences in the death rates between birth and maturity of children born to cousin marriages as contrasted to those observed in children born to unrelated parents, Böök (1957) in a smaller sample studied in Sweden observed no such differences. One partial explanation for the magnitude of the difference between these two studies might lie in the fact that in the study of Sutter and Tabah (1952, 1953),

the authors personally interviewed the parents in the consanguineous marriages, whereas their information concerning the outcome of the control, non-consanguineous marriages came from the village clerk who, although undoubtedly well informed, was probably somewhat less informed than the parents themselves. Fortunately, it is not necessary to choose between or average these somewhat conflicting results, since Schull (1958) has provided similar data, although for a much more limited time span, for the Hiroshima and Nagasaki populations. With respect to survival through roughly the neonatal period, the ratio of "inbreeding" to "random' load is similar to that encountered in France. A detailed discussion of the differences between the French study and that conducted in Japan will be found in Schull's paper. Because of the several differences there listed, as well as the possibly higher coefficient of inbreeding in Japan in recent centuries, it seems unwise to attempt to reach conclusions at present as to whether this correspondence indicates that the French figures are more nearly characteristic for European populations than those from Sweden. For congenital defects in Japan, Schull (1958) has calculated that the ratio of "inbreeding" to "random" load is, for the cities of Hiroshima, Nagasaki, and Kure, approximately 10:1. If we may use the term "malformation equivalent" in the sense that Morton, Crow, and Muller (1956) employ the term "lethal equivalent," then this ratio is somewhat less unfavorable to attributing a significant role to balanced polymorphic systems than the 17:1 ratio which prevails in the French data for deaths prior to the age of reproduction.

There exists a second line of reasoning relevant to the question of whether the inbreeding data presently available are consistent with balanced polymorphic systems playing a significant role in congenital defect and early death. A balanced polymorphic system contributes equally to the "random" and "inbreeding" loads only when the system is composed of but two alleles. However, the majority of polymorphic systems quite likely involve multiple alleles and, in the specific instance under discussion, also multiple loci. Crow (1958) has demonstrated that in the case of multiple alleles in a balanced polymorphic system, the contribution to the inbreeding load is greater than to the random load, in proportion to the number of alleles involved. In view of our ignorance concerning the number of alleles involved in polymorphic systems, the allowance to be made for this factor in interpreting inbreeding effects is uncertain, but perhaps should be considerable.

A second factor to be considered in interpreting inbreeding results is that the systems concerned—at least as here postulated—involve several loci. The type of inbreeding effect to be expected depends to a large extent on the precise nature of the model selected. If, for instance, one elects a two-locus model with only a single pair of alleles at each locus, one much less common than the other, the "phenodeviant" being the double recessive, a consanguinity effect is expected, whereas if one elects a five-locus model with a single pair of equally frequent alleles at each locus, but the "phenodeviant" resulting when an individual accumulates five "recessive" alleles in any combination, then a consanguinity effect is not anticipated. But if one modifies this latter model so that one of the "recessive" alleles is rare and essential in the homozygous condition to the development of the phenodeviant, then the locus involved "controls" the appearance of the phenodeviant to a large extent, and a consanguinity effect is to

be expected. In view of our ignorance of multigenic homeostatic systems in experimental animals, it does not seem profitable to explore various artificial models further.

Attention has been directed to the possibility that fatal congenital malformations are less frequent in the American Negro than in Caucasians. The ancestry of the American Negro is approximately one-third Caucasian. The possibility must be entertained that in the centuries since the separation of Caucasian and Negro lines of development, similar-appearing malformations have come under the control of different genetic systems. The relatively recent large-scale hybridization of Negro and Caucasian may have disturbed long established genetic equilibria. To take the simplest possible example, if a given phenotype were due to homozygosity for gene *a* in one population, and for a non-allelic gene *b* in another population, hybridization of these two populations will, for most genetic models, result in a decrease in the frequency of the phenotype. Studies on "pure" Negro populations will be of great interest, since if the above suggestion is correct, then the total frequency of congenital malformation in such pure populations should be closer to Caucasian and Japanese values than is the case for the American Negro.

One measure of the value of a hypothesis is the research which it suggests. A critical evaluation of the genetic concept of congenital defect suggested in this paper requires that the organism chosen for testing the hypothesis be susceptible to selective breeding experiments, and, ideally, that the species be sufficiently well known genetically that the segregation of marked chromosomes can be followed. Neither of these conditions is met by man. Argument by analogy from experimental material is likely to be of importance here for some time to come. To the best of the author's knowledge, no one has attempted to analyze the genetic basis of an "unselected" series of malformations in any species. Because of the emphasis in the past on "clean" genetic characters, it seems quite likely that although many attempts have been made to establish strains of animals with particular congenital defects, as a rule only those strains have been preserved which responded most quickly to selection. Since the smaller the number of genes involved the more gratifying the response to selection, this will of course tend to give a biased view of the total picture.

Lerner (1954) has marshalled the evidence for the existence of homeostatic genetic systems in various animal species, and no attempt will be made here to duplicate that discussion. However, among recent investigators, the important contributions of Landauer (1947, 1953, 1955, 1956, and 1957) on malformations in the chicken are especially relevant to the present discussion. The chicken offers unusual advantages to the study of the role of genetic factors and their modification by environmental influences in the etiology of congenital malformations, since in addition to the fact that it is a relatively fast-breeding animal separated into many strains, the environment of the developing embryo may be manipulated in a variety of ways not possible for mammals, and the results of that manipulation also more easily observed than in mammals, where the *in utero* resorption, or at least autolysis, of defective embryos which die during development, and the tendency of some laboratory animals to devour defective young, introduces real problems. Strain differences among chickens in their responses to teratogenic agents can be readily demonstrated (Landauer, 1947,

1953). Strains which respond to a particular teratogenic agent with a high frequency of a particular defect are often found to exhibit spontaneously a relatively high frequency of that particular malformation (Landauer, 1955, 1956). Genetic analysis of one such malformation, the rumpless trait, suggested that the responsible gene or genes were widespread but kept from manifestation by equally widespread "suppressor" genes (Landauer, 1955). In discussing this, Landauer (1955) has written:

> "If similar evidence can be obtained with other material, it should become possible to test, and perhaps verify the hypothesis that the occurrence of sporadic malformations with typical stock frequencies and with characteristic strain differences in response to experimental conditions are brought about by hereditary factors which ordinarily are insufficient to interfere with normal development, but which may become a part of the hereditary mechanism for polyfactorially transmitted traits."

The pertinence of these observations to the problem of human congenital malformations is obvious. In the light of the preceding observations, the question at once arises whether the "suppressor" genes are there solely to suppress the appearance of certain phenotypes—a point of view which if carried to its logical conclusion implies that a considerable proportion of the germ plasm is engaged in the "suppression" of a considerable other proportion—or whether, rather, both the "suppressor" and "suppressed" genes are there for a common reason, as elements in a homeostatic system involving many loci.

At this point we may return with profit to consider the significance of the tendency of major defects to be associated with one another. This association can be attributed to the action of genes with pleiotropic effects. However, the demonstration (p. 430) that these associations in many instances reflect the incidence of the specific defects concerned in the populations as a whole suggests an alternative interpretation. If we regard some congenital defects as being the result of certain zygotes receiving through segregation (either from simple genetic systems or from more complex homeostatic, polygenic systems) one or more genes of such a type that a threshold necessary to congenital defect is exceeded, then, as has been brought out previously, age-parity effects indicate the lability of this threshold. It seems reasonable to postulate that the individual's genetic constitution may also influence this threshold. One may accordingly argue that anencephalics and hydrocephalics also have harelip and/or cleft palate more often than normal infants, and in different populations in proportion to the frequency of harelip and/or cleft palate in the population, simply because the constellation of genes leading to anencephaly alters the threshold for the expression of the harelip gene-complex, a gene-complex which on the basis of the association figures would appear to be rather widespread. In point of fact, it is almost certainly not a matter of one gene constellation lowering the level of expression of another so much as an interaction phenomenon which alters the level of expression of both. We see here, then, some confirmation for the point of view adopted earlier in the attempt to reconcile the non-concordance as regards major defect in identical twins with the other evidence implicating genetic factors in the etiology of congenital defect. It has previously been noted that consanguinity effects seem particularly evident with respect to children with multiple malformations. Pursuing this same line of thought, it

may be postulated that the mutual lowering of the threshold of phenotypic expression postulated as an explanation for the association of multiple major defects is facilitated against the background of the greater homozygosity resulting from consanguineous marriage. If this viewpoint concerning the significance of the association of major defects is correct, it has important implications for the economy with which populations meet the problem of segregation from either simple or homeostatic, polymorphic genetic systems. This "synergism" of gene action implies that one defective individual may serve as the vehicle whereby a population eliminates the *potential* phenodeviants resulting from the segregation of a number of different genetic systems. In the particular example under discussion, anencephaly is so lethal that the addition of a harelip in nc way alters the likelihood of survival. With other, semi-lethal defects, however, the presence of two defects might well significantly alter the likelihood of survival and reproduction, by comparison with the situation when only one is present.

Numerous authors have remarked on the unusual sex ratios encountered in various series of specific defects (cf. Woolf, 1946). Thus, imperforate anus is notably more common in male infants, anencephaly in females. The question of the sex ratio in this material will be made the subject of a separate paper. Suffice it to say here that departures from equality with regard to the sexes affected can be interpreted as another manifestation of the interaction of different genetic systems invoked above to account for the association of major defects.

The need for appropriate studies on a suitable laboratory animal, if we are ever to understand the importance of homeostatic systems in the etiology of congenital defect, is clear and pressing. The need for further studies on man is equally clear. Thus, Penrose (1955) and Vogel (1956) have emphasized the extent to which studies of paternal age effects can delineate the role of mutation in such phenomena as congenital malformations. The findings in this particular study on this subject will be described later (Schull and Neel, in manuscript). It seems clear that by the judicious combination of this approach and the approaches described in the present communication, as well as careful follow-up studies on the reproductive behavior in individuals with congenital defect, there is every prospect of an early clarification of the existence and mode of action of genetic and non-genetic factors in the etiology of congenital defect. Inasmuch as the non-genetic factors responsible for the occasional phenotypic manifestation of what have been postulated to be widespread genotypes may range from a transitory exposure of the pregnant female to a noxious chemical to an unrecognized viral disease, the need for the team approach to this problem is obvious.

X. SUMMARY

1. The frequency of major congenital defects in Japanese infants born to non-consanguineous parents, as revealed by physical examination shortly after birth, was found to be 1.02 per cent among 64,569 births occurring in Hiroshima, Nagasaki, and Kure between the years 1948 and 1954.

2. Among a total of 9 twin pairs, 7 of like-sex, ascertained because of the occurrence of major congenital defect in one member of the pair, there were no instances of concordance as to the occurrence (or type) of defect.

3. Post-mortem examinations of 264 children who were stillborn or died during the neonatal period and who came to autopsy in Hiroshima without the clinical diagnosis of major defect revealed that 10.2 per cent of them had internal defects of major proportions.

4. Among 4,845 children born to consanguineous parents in these cities during this same period, 1.42 per cent were found to have major defect.

5. It is estimated that the total frequency of major congenital defect among all the Japanese infants comprising this sample (both those of consanguineous and non-consanguineous origin) would be 1.37 per cent, if all children who were stillborn or died during the neonatal period were subjected to a post-mortem examination.

6. Re-examination of 16,144 infants at age approximately 9 months revealed an additional 1.75 per cent of infants with major congenital defect, bringing the estimated total of major congenital defect to 3.12 per cent.

7. Evidence is presented indicating slight but significantly increased recurrence risks within a sibship where a child with a congenital malformation has been born, the risks being of a malformation-specific type.

8. Different major defects manifest a significant tendency to be positively associated with one another. It is suggested that the extent to which these associations occur reflects, but in a disproportionately positive manner, the frequencies of the specific defects in the population concerned.

9. From a comparison of these data with the available information on congenital malformations in Caucasian and Negro populations, it becomes apparent that the biological impact of congenital malformation is very similar for all populations where it has been measured accurately, far more so than for almost any other important cause of death, although from population to population, despite the similarity in the total impact of congenital malformations, there tend to be numerous differences in the frequency with which specific malformations occur. These facts plus the other lines of evidence just enumerated, are considered to point towards the possibility that a significant fraction of human congenital defects are the segregants (phenodeviants) resulting from the existence and functioning of complex (multi-local) genetic homeostatic systems, of the type particularly discussed by Lerner (1954). The existence of significant age-parity effects on the frequency of congenital defect raises the possibility of influencing to a considerable extent the phenotypic manifestations of these systems, but only at the risk of shifting long-established genetic equilibria.

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Consanguineous Marriages in the Chicago Region[1]

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AMONG THE PROBLEMS in the study of human genetics is the appraisal of the "load of mutations" that is carried by an average man. The children of a consanguineous marriage will have a greater than average chance of receiving the same rare recessive gene from both of their parents. This situation occurs because the common ancestors of the parents might have carried and transmitted to both parents various rare genes. In this paper we will estimate from the increase of deaths and abnormalities in consanguineous families the average number of rare recessive genes present in a human being.

The study of consanguinity has a long history, with its scientific aspects going back a century to the work of Bemiss (1858). Bemiss clearly saw that his data were influenced by selection, that is, that he would be told of the children of consanguineous persons more frequently if they were abnormal than if they were normal. Since that time, various authors have attempted to avoid this type of bias. Mitchell (1865) employed both of the methods that have since proven successful for others: (1) he made a study of all marriages in a given population, locating the consanguineous ones in that manner, and (2) he studied the ancestry of all persons with a certain ailment (lunacy) in a large area.

In the Roman Catholic Church, close consanguinity is an impediment to marriage. A dispensation is required before an ecclesiastically valid marriage is possible. Utilizing this fact, Orel (1935) introduced a refinement of Mitchell's first method by locating consanguineous marriages through the records of dispensations in the Roman Catholic Archdiocese of Vienna. Similar investigations have been carried out in France by Sutter and Tabah (1952) using the records of the Dioceses of Blois and of Vannes.

SOURCES OF THE DATA

This study has been made with the help of the records of the Roman Catholic Archdiocese of Chicago. Records of dispensations from the impediment of consanguinity to marriage (*impedimentum consanguinitas in gradu secundo*), have been obtained for the twenty years between 1936 and early 1956. Information on 239 marriages was gathered in this manner. Of these, 78, or one-third of the families, were not available to us because either, as in five cases, they refused an interview, or they are known to have moved to another part of the country, or else their present whereabouts are unknown.

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Not all of the remainder of the marriages have proven useful for this study. Because of the small numbers concerned and the loss of information with increasing distance of relationship, the 17 families in which the relationship was more distant than that of first cousins have been omitted. In 12 additional families the relationship was one of affinity (relationship through marriage), rather than consanguinity.

In 23 marriages there was little likelihood of children from the outset because of the advanced age of one or both of the participants. These have been omitted, as was one case in which the exceedingly poor health of the wife probably precluded consummation of the marriage. Seven additional cases were referred to an interviewer by their pastors at the time that the pastors were being consulted about cases in the Archdiocesan files. Because their irregular ascertainment probably does not bias the pertinent information about them, these cases have been included in this study.

In many cases, the marriage ceremony had been a religious validation of a previously contracted civil marriage. We decided to limit this work to the consideration of marriages contracted since 1920, as many of the data analyzable in this investigation (e.g., medical care of children) were very different after World War I from what they had been in the years previous to it. Fortunately, only six families had to be discarded because their civil marriage took place prior to 1920.

All subsequent statements are based on the remaining 109 consanguineous families. Of these, 106 are marriages between first cousins, one is a marriage between double first cousins, and there is one uncle-niece and one aunt-nephew marriage. Among the 107 consanguineous families for which adequate data exist, 25 had a civil marriage at least one year prior to the religious validation of the marriage and in five additional cases they lived together as man and wife for some time without formal marriage.

During the interview of each consanguineous family, a brief description was made of the sibships of the husband and wife. A control interview was then arranged with one of the married sibs. To decrease selection in choosing the control, preference was given to an interview with a sister of the wife, and 50 controls of this type were obtained. Sometimes the wife did not have a married sister in the Chicago area, hence there were 32 additional controls where a sib of the husband or brother of the wife was used. In one instance, the control is a nephew of the wife. This gives a total of 83 control families. Most of the 26 other families did not contain sibs who could be used as controls. In a few cases, the consanguineous couples requested us not to derive a control from their immediate relatives.

The children of consanguineous marriages will be referred to as consanguineous children. The children of control marriages will be referred to as control children. The control and consanguineous children are related to each other both as first and as second cousins (e.g., if the consanguineous and control wives are sisters, then their children are first cousins. In this event, the husband in the consanguineous family is a first cousin of the wife in the control family and through this relationship the children are second cousins.). Because of the close relationship, the two groups of children are likely to represent a similar socio-economic status, which, it is hoped, would be reflected in similar medical care.

The interviews were carried out in the homes of the families concerned. The interviewers (R.H.R. and R.E.H.) are Catholic priests. They introduced themselves as priests and pointed out the statistical nature of the study and the fact that only they would know the source of the information. Almost without exception, they received full cooperation from the families.

For one consanguineous family the interview was conducted by mail. Information on another family was obtained from the parents and a sister of the husband. The information on one control family was supplied by the consanguineously married woman, who described her sister's family. These three families live in other parts of the country. Thus, for only one consanguineous and only one control family was there a failure to get information directly from one of the parents.

In general, the control couples were interviewed about a year after the consanguineous couples.

For some of the data, a special control population has been derived from that portion of the records of Cook County, Illinois, which concerns the city of Chicago. Selection was made of couples married during 1936 whose last name begins with the letter *A* and for whom there was an indication that the marriage had been performed by a Catholic priest. The distribution of consanguineously married couples by national origin probably is not random within the Catholic population of Chicago, as will be noted later. Family names beginning with the letter *A* have similar biases with respect to national origin. Birth records were searched for the succeeding nine years and the 133 families for which a subsequent first birth has been recorded have been used for certain items of information. This control group will be referred to as the county-records control.

RESULTS

Statistics of consanguineous marriages

The relatively low frequency of consanguineous marriages currently taking place in the United States may be seen from studies of Woolf *et al* (1956), who found somewhat less than one first-cousin marriage per thousand among Mormons and their non-Mormon relatives in the period since 1940. Their data indicate that over the past two centuries the frequency has declined with some regularity from a value about ten times the present rate. About half of the decrease has taken place in the last half century. Statistics do not appear to be available on the frequency of first-cousin marriage among American Roman Catholics relative to the population as a whole.

In figure 1 are given the numbers of marriages between first cousins observed each year since 1936. The year when first married is given as the year of marriage (if civil marriage preceded religious marriage), or, in the four pertinent cases, the year in which cohabitation without any marriage ceremony began. This method has been employed on the assumption that almost all of these marriages would have been under religious auspices from the beginning if it were not for the fact of consanguinity. Data on the number of marriages commencing prior to 1936 are incomplete and therefore have not been presented. Also shown in figure 1 for certain years are the

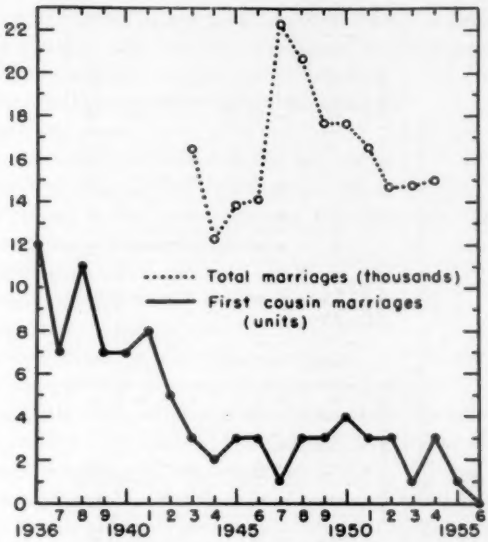

FIG. 1. The observed number of first-cousin marriages of the type discussed in this paper and the thousands of all marriages performed under the auspices of the Archdiocese of Chicago, Illinois, 1936–1956.

thousands of marriage ceremonies performed (dotted line) under the auspices of the Archdiocese of Chicago, as listed in The Official Catholic Directory (1943–1954). The first-cousin marriages are underrepresented because of the factors which militate against a religious ceremony for them and also as a result of the fact that not all first-cousin marriages have been included here (marriages involving elderly persons, and untraced and uninterviewed couples have been omitted). Figure 1 is so drawn that agreement of the two lines would indicate a frequency of one-tenth of one per cent for first-cousin marriages. Allowing for some additional cases to correct for underrepresentation, it appears that first-cousin marriages of the type discussed in this paper were at a level of less than one-tenth of one per cent at the beginning of this period and that they now are less frequent than one-twentieth of one per cent of all marriages in this Archdiocese.

National origins

Table 1 lists the major nationality groups represented among these consanguineous marriages, the nature of the consanguinity, and the number of liveborn children in each marriage. The marriages have been listed in the nationality category that provided the common ancestry. The "Other" group includes families of which there are three French or French-Canadian, two Mexican, one Puerto Rican, one Lebanese, one Norwegian, one Negro, one "old American" and two of unascertained national origin. Also shown in table 1 is the relationship between the consanguineous marriage

TABLE 1. NATIONALITY DATA AND NUMBER OF LIVEBORN CHILDREN AMONG THE CONSANGUINEOUS AND CONTROL FAMILIES

National origin	Type of consanguineous marriage*						Liveborn children							Control relationship*						Control Spouse of other National Origin	Liveborn Children							
	Total	1	2	3	4	other	0	1	2	3	4	5	6	Total	1	2	3	4	Other		0	1	2	3	4	5	6	8
Italian	45	7	16	8	12	U-N, A-N	9	11	17	6	2	—	—	35	5	21	3	5	1	8	4	8	17	5	1	—	—	—
Polish	18	5	5	4	4		5	5	4	2	—	2	—	15	1	10	2	2	—	4	1	5	3	4	2	—	—	—
Other East European	8	2	2	1	—	1 double first 2 unknown	—	3	3	1	1	—	—	3	2	1	—	—	—	—	2	—	1	—	—	—	—	—
German	13	3	5	5	—		2	1	6	2	—	2	—	11	—	9	—	2	—	9	1	2	2	1	1	1	2	1
Irish	13	3	5	3	2		3	1	4	2	—	3	—	9	2	4	1	2	—	7	2	1	5	—	1	—	—	—
Other	12	3	6	1	2		1	2	2	3	2	1	1	10	1	5	1	3	—	7	2	—	5	2	1	—	—	—
Totals	109	23	39	22	20	5	20	23	36	16	5	8	1	83	11	50	7	14	1	35	12	16	33	12	6	1	2	1

* See text for explanation of code.

and its control, the number of marriages in which the control propositus married a person of another national origin, and the number of liveborn children in each marriage. The type of consanguineous marriage is coded as:

(1) the husband's father and wife's father are brothers
(2) their mothers are sisters
(3) the husband's father and wife's mother are sibs
(4) the husband's mother and wife's father are sibs

The controls are related to the consanguineous families as the families of:

(1) the consanguineous husband's brother
(2) the consanguineous wife's sister
(3) the consanguineous husband's sister
(4) the consanguineous wife's brother

For the aunt-nephew marriage, the only satisfactory control was one of her other nephews, which accounts for the remaining control family.

It is possible that the high frequency of persons of Italian ancestry (who appear to form a much smaller proportion of the Catholic population of Chicago) is a reflection of the high frequency of consanguinity in Italy (Adamo, 1952).

It will be observed in table 1 that type 2 consanguineous marriages are about twice as frequent as those of any other type, the variation from a uniform frequency being significant ($\chi^2 = 8.85$, 3 d.f., $P < .05$). The observed frequencies of the four types of marriage are roughly the same for Italians and non-Italians ($\chi^2 = 4.23$, 3 d.f., $P > .05$, for Italian vs. non-Italian couples for the four types of first-cousin marriage). The other nationality groups do not show striking departures from the general pattern. The frequencies of the various types of marriage may be compared with those cited by Morton (1955). The excess of type 2 marriages is similar to that shown for the Japanese and Austrian data, but an excess of type 4 marriages has not been observed by us.

Most of the consanguineously married persons were born in the United States. In eight marriages both parties were born in another country, in 21 cases only the husband was born abroad, and in 13 cases only the wife was born abroad. Among the controls, eight couples were both born abroad, in 11 cases only the husband was born abroad, and in two cases only the wife was born abroad. The correlation between sibs in the control and the consanguineous groups and the selection for residence of controls in the Chicago area vitiate any statistical analysis on the proportion of foreign-born individuals in the two groups. Furthermore, an analysis with respect to the proportion of foreign born of marriageable age in the United States would be inadequate with the data that are available.

Marital status

In the consanguineous families, men of 29.4 ± 6.1 years of age (mean $\pm$ standard deviation) married women of 24.6 ± 5.2 years of age (based on 108 families). Among the control families marriage is earlier, men of 26.8 ± 4.8 years having married women of 22.8 ± 4.0 years (based on 82 families). The value of t for the difference between the mean age at marriage for each sex is highly significant ($P < .01$), being 3.29 for the men and 2.68 for the women. The analysis has not been made with any correc-

tion for the skewing due to the occurrence of a long tail toward the older individuals. The median age at marriage is slightly less in all groups, but the difference in age at marriage remains at 1.8 years for the women, though the mean difference, 2.6 years, decreases to a difference of 2.3 years in the median for the men.

The correlation between the ages of husband and wife at time of marriage is .67 for the consanguineous couples and .57 for the controls. The difference between these values is not significant. In about ten per cent of both groups the husband is younger than the wife.

Among the consanguineous families, four persons had previously been married. One man had a childless civil marriage, one man had been widowed with one child, one woman had been widowed with one child, and one woman had a previous marriage with one child. In an additional case, one of the women is raising an illegitimate child born before her marriage. Among the controls, the first marriage of the propositus has been used. The spouses of these propositi include one woman and two men who have previously been married but who did not have any children, one woman with a child by a previous marriage, and one woman with an illegitimate child born prior to marriage.

Among the 109 consanguineous families, seven marriages have been terminated by separation or divorce and seven by the death of one of the spouses. Among the 83 controls, six have been terminated by separation or divorce and seven by death. For all four of these groups of terminated marriages, about half of the families concerned were still within the age period during which one or more additional children might have been anticipated.

Not all of these investigated families have completed their child-bearing period. Forty of the consanguineous women and 27 of the control women have had a pregnancy terminate within the six years preceding the interview, which is an indication that a moderate proportion of the families will probably have one or more additional children. To the extent that abnormal children are positively correlated with parental age or birth rank, this failure to have complete families will introduce a bias into these observations so that the observed proportion of abnormal children may be a bit below the true proportion for these families.

Pregnancy

During the interview, each woman was asked about her children, and, at a later stage of the interview, about any dead children or lost pregnancies. The informant's statements about miscarriages or stillbirths have been used without question, although by some definitions a few of the miscarriages might be termed stillbirths.

Tables 2 and 3 indicate the pregnancy wastage in the consanguineous and control families, respectively. The families listed above the stepped line are those in which all pregnancies have resulted in live births. Seventeen consanguineously married women have not had any pregnancies, 68 have had a liveborn child at each pregnancy, and 24 have lost one or more pregnancies. All pregnancy losses were miscarriages except for three stillbirths. One woman had five pregnancies of which one was a live birth, one a stillbirth, and three were miscarriages, and one woman had one liveborn child and two stillbirths. Among the controls, 11 women have had no

TABLE 2. THE NUMBER OF PREGNANCIES AND LIVE BIRTHS AMONG THE CONSANGUINEOUS FAMILIES

Live births	0	1	2	3	4	5	6	7
6							—	1
5						4	1	3
4					2	2	1	—
3				11	5	—	—	—
2			31	2	2	—	1	—
1		20	1	1	—	1	—	—
0	17	2	—	1	—	—	—	—

Pregnancies

TABLE 3. THE NUMBER OF PREGNANCIES AND LIVE BIRTHS AMONG THE CONTROL FAMILIES

Live births	0	1	2	3	4	5	6	7	8	9	10	11
8									—	—	—	1
7								—	—	—	—	—
6							—	2	—	—	—	—
5						—	1	—	—	—	—	—
4					5	1	—	—	—	—	—	—
3				8	3	1	—	—	—	—	—	—
2			28	3	1	—	1	—	—	—	—	—
1		12	3	1	—	—	—	—	—	—	—	—
0	11	1	—	—	—	—	—	—	—	—	—	—

Pregnancies

pregnancies, 53 have had a live birth at each pregnancy, and 19 have lost one or more pregnancies. Of the lost pregnancies, a stillbirth occurred to one of the women who lost one of two pregnancies. For one of the women who lost one of seven pregnancies, the loss was of a stillborn child, twin to a premature infant who died soon after birth.

The frequency of families in which the female has never been pregnant is .1560 (17/109) among the consanguineous and .1325 (11/83) among the controls. These frequencies do not differ significantly. However, the analysis of the data is improved by considering only those childless marriages for which the length of marriage has been sufficient to show that children are not likely to occur. Although 15 of the sterile consanguineous couples have been married and remained together for ten or more years, only five of the sterile control couples have been married this long. Correcting for the incompletely observed couples, 15 of 107 consanguineous couples have not had any pregnancies, whereas only 5 of 77 control couples have not had any pregnancies. This difference is not significant ($\chi^2 = 1.90$, 1 d.f., $P > .05$. All χ^2 tests with one degree of freedom have been corrected for continuity). Many of the parents stated that they had heard that consanguinity has deleterious effects on the children. The extent to which these beliefs may have affected the fertility of these families is unknown. Most of the sterile families have expressed great regret over their sterility.

It is possible that the sterility observed has been conditioned by the age at mar-

riage. As previously noted, a number of marriages have been omitted from consideration because of the age of the contracting parties. These have included all sterile marriages in which the wife was at least 36 years old at the time of marriage. Also omitted was one marriage in which the husband was described as too old to have children. Even though these cases had been removed, the median age at marriage of the sterile women was about two years greater in each group than the median age at marriage of those women who have become pregnant. These differences are not significant.

A small bias toward early marriage is effected by the marriage of women who become pregnant prior to marriage. The marriage and birth data in the county-records control may aid in understanding the magnitude of the effect of premarital pregnancy on marriage fertility. In seven of the 133 cases, a child was born within the first seven months of marriage. This suggests that for the population being studied in this paper the frequency of pregnancy at the time of marriage is of the order of five per cent. This could account for only a small difference between fertile and sterile women in age at marriage. Furthermore, the small number of sterile women dealt with in this report does not indicate with any certainty that the apparent lateness of their marriage is other than a chance deviation.

Twenty-three of the consanguineous women have had a total of 36 miscarriages. Thus .2500 of the 92 fertile women have had one or more miscarriages and .1452 of the total of 248 pregnancies have resulted in miscarriage. There have been 25 miscarriages among a total of 17 control women. This gives one or more miscarriages among .2361 of the 72 fertile women and .1289 of the total of 194 pregnancies have ended in miscarriage. By both criteria the differences are slightly in favor of the control women, but are not significant. *If* there is a correlation between miscarriage frequency and age, the slightly greater age at marriage of the consanguineous women might account for the differences observed. The woman's statement as to the approximate age of the fetus at the time of the miscarriage has been used in the compilation of table 4.

The three stillbirths observed among the consanguineous families do not differ significantly from the two stillbirths observed among the control families.

We have previously suggested that the existence of very early fetal deaths could profitably be looked for in investigations into consanguineous marriages (Slatis and Reis, 1956). If there is a class of lethal genes which acts so soon after conception that the fact of conception is not even recognized, this might be observed as a delay in the average time between marriage and the birth of the first child or as an increase in the interval between the births of two children of adjacent birth rank. Because of the difficulty of gathering information on the pregnancies resulting in other than liveborn children, only live births have been considered. For firstborn children, correction must be made by the omission of those born before the eighth

TABLE 4. LENGTH OF GESTATION OF MISCARRIAGES

Months.....	1	2	3	4	5	6	7	Unknown	Total
Consanguineous	2	8	17	4	1	1	2	1	36
Controls	5	5	9	3	—	2	—	1	25

month of marriage. Among the consanguineous families, adequate data exist for 71 firstborn children. The median time to first birth is 17.7 months. Sixty-five control families can be used for this study. The median time to first birth is 23.7 months. These values cannot be considered as differing significantly. It should be noted that, contrary to expectation, the consanguineous group had the shorter median time to first birth. In the county-records control, the 126 qualifying families showed a median of 21.5 months between marriage and the birth of their first child. This interval is between the values observed for the two interviewed groups.

The difficulties associated with establishing the date of marriage do not exist for the time interval between the birth of the first and the second child. The 64 consanguineous families supplying adequate data show 27.5 months between the first two liveborn children, whereas among the 55 related controls the first two children are separated by an interval of 36.5 months. Here again, the difference is not great enough to be considered as other than chance variation and it is in the direction contrary to that expected. Thus, the search for early lethals is negative.

Liveborn children

The consanguineous couples have had a total of 209 liveborn children of which 107 have been boys and 102 girls. The 167 liveborn control children include 90 boys and 77 girls. The sex ratio in the two groups is very similar ($\chi^2 = .17$, 1 d.f., $P > .05$) and there is no significant difference from the usually reported sex ratio for a U. S. white population (51.5 per cent boys). The numbers of children per fertile family are almost identical, being 2.27 for the consanguineous and 2.32 for the controls (note that many families are not yet complete, so that the true family size may be somewhat greater).

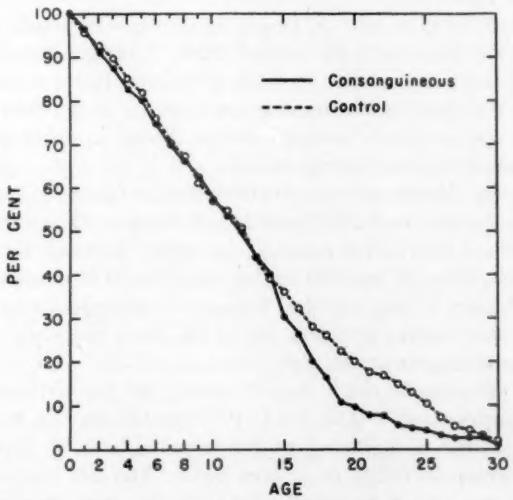

FIG. 2. The percentage of living consanguineous and control children who exceeded a given age at the time of interview.

Figure 2 is a representation of the age of the living children at the time of interview. A cumulative graph has been used so that the proportion of children that are as great or greater than any given age may be read directly (e.g., about 70 per cent of the children in each group are seven years old or older). Up to the age of 14, the two curves agree very well. Thus, for conditions with an age of onset less than 14, the proportion of each group that has passed through this period is the same. About one-third of the consanguineous marriages took place between 1936 and 1938, and because of this, about 30 per cent of the consanguineous children were between their 14th and 19th birthdays at the time of interview. The control families, having married a bit before or a bit later than their sibs, have their children more evenly spaced in this period. Since almost no observation in this paper is dependent upon conditions with an age of onset greater than the 14th birthday, this difference is of little consequence. The difference indicates, however, that a greater percentage of the control children was born over 20 years ago, and, to the extent that medical techniques were improving during that period, the control children experienced a slightly greater risk of childhood death than did the consanguineous children.

Infantile and childhood death

Seventeen of the consanguineous children have died. Four died within the first week of life and the other 13 died at various ages up to ten years. None of these deaths has been attributed to accidental causes other than injury at birth. In addition, one consanguineous child is known to have died after the interview (age 20). Death was attributed to a brain hemorrhage, and a minor injury received several years earlier has been implicated as a contributory factor. This death is not included in this study. Only four of the control children have died, three on the day of birth and one at the age of one year.

These deaths are listed in table 5. Death certificates were sought for all of them and were found for those noted by a check mark. A further check mark indicates than an autopsy was recorded on the death certificate. In those cases for which a death certificate was observed, the remarks are based on its statements except where otherwise noted. Except for the neonatal deaths, the age at death is not accurately known if the death certificate was not found.

The case of cystic fibrosis and von Gierke's disease (glycogen storage disease of the liver) are attributable to the action of recessive genes. The sixth child in family 11 died of a condition described as muscular dystrophy. Although the autopsy record for the fifth child makes no mention of this condition, it is possible that the first, fifth, and sixth children in family 11 died because of homozygosity for the same gene. It is likely that other deaths were also due to the effect of specific recessive genes, but this is not ascertainable at this time.

The observed difference in death rate, 17 among 209 live births as opposed to 4 among 167, is significant ($\chi^2 = 4.76$, 1 d.f., $P < .05$). In addition to this, one of the consanguineous children is moribund, as will be noted later, so that the frequency of death in this group is certain to go even higher. The fact that the 17 observed deaths represent only 12 families may be indicative of non-randomness with respect to mortality. Non-randomness of this type would be expected on genetic grounds,

TABLE 5. DEATHS OF LIVEBORN CHILDREN

TABLE 5. DEATHS OF LIVEBORN CHILDREN

Consanguinity	Family	Live births	Miscarriages	Stillbirths	Birth rank	Sex	Death certificate	Autopsy	Age			Year of death	Cause of death stated on the death certificate, and remarks
									Years	Months	Days		
+	1	2	0	0	1	F	✓	—	0	1	1	1951	Peritonitis due to bowel obstruction and adhesions. Surgery performed.
+	2	2	0	0	1	F	✓	—	5	5	4	1956	Cardiac failure due to cystic fibrosis, pancreatic and pulmonary.
					2	F	—	—	2	6	—	1954	Parents state child had cerebral palsy as a result of birth injury.
+	3	2	0	0	1	F	✓	✓	0	9	19	1949	Pertussis, bronchopneumonia, diarrhea.
+	4	3	1	0	2	F	✓	✓	0	0	1	1950	Congenital pulmonary atelectasis. Parents state infant had harelip; premature.
					3	M	✓	✓	0	5	3	1953	Bronchopenumonia. Parents state infant was spastic.
+	5	4	0	0	4	M	✓	—	0	0	4	1956	Inanition and cachexia. Premature. No malformations.
+	6	4	2	0	1	F	✓	✓	1	5	25	1925	Left lobar pneumonia. Contributory: myocarditis.
+	7	5	0	0	1	M	✓	—	2	9	0	1941	Cardiac failure due to marasmus due to congenital glandular dystrophy. Operations for congenital cataract. Parents state child did not speak.
+	8	2	0	0	1	M	—	—	0	0	1	1938	Parents state there was a brain injury at birth.
+	9	5	0	0	3	M	✓	✓	0	1	4	1947	Inanition due to von Gierke's disease involving liver, kidney and heart.
+	10	5	1	0	1	F	✓	—	3	1	9	1941	Bronchopneumonia due to measles.
+	11	6	1	0	1	F	—	—	1	—	—	1939	Parents state child had convulsions and that all teeth erupted simultaneously.
					2	M	✓	—	10	1	5	1950	Organic heart disease of five hours duration.
					5	F	✓	✓	0	9	28	1949	Bronchopneumonia.
					6	F	✓	—	0	7	12	1956	Muscular dystrophy. Parents state convulsions occurred.
+	12	2	0	0	2	F	✓	✓	0	0	4	1943	Fusion of pulmonary artery and aorta; interventricular septum defect; large patent foramen ovale.
—	13	2	0	0	2	F	✓	—	0	0	0	1946	Intracranial hemorrhage (birth injury).
—	14	4	0	0	2	M	—	—	0	0	0	1940	Cause not known.
—	15	6	0	1	3	F	✓	—	0	0	0	1946	Premature, placenta partialis. Parents state infant was twin to a stillborn male.
—	16	2	0	0	2	M	✓	—	0	11	22	1939	Bronchopneumonia following a cold and bronchitis.

but an adequate analysis of it awaits a greater number of cases. There is, to some extent, a self-augmenting feature in this non-randomness, since early deaths may play a role in bringing forth more children as replacements (see, for example, Glass, 1950). Thus, the last child in family 11 was born after the deaths of three of her sibs, and it may be relevant that this, the consanguineous family with the largest number of liveborn children (six), has never had more than four living children at any time. Also, the frequency of death among the consanguineous families having four or five liveborn children is greater than among the smaller families.

The male:female ratio of 6:11 among the dead consanguineous children does not differ significantly from 1:1. As will be seen among children with serious ailments it is the boys who are more frequently affected.

Abnormalities and ailments

The various infrequently occurring abnormalities and ailments of the living children have been listed in tables 6 and 7. Thirty-one of the consanguineous children are listed (no child is listed twice), but only 16 of the control children have been found to have complaints of a similar nature ($\chi^2 = 2.55$, 1 d.f., $P > .05$, not significant). The male:female ratio is 23:8 for the consanguineous and 9:7 for the controls. If the listing had been limited to those children whose abnormalities have seriously interfered with the processes of a normal life, eight of the consanguineous children (all boys) would be included but none of the controls ($P = .007$ by Fisher's exact method, significant, that a deviation of this magnitude will be found in this direction). The tables are divided into (1) ailments requiring special care over a long period of time, (2) less serious ailments, and (3) uncommon infections and their sequelae. Only the last two categories occur among the control children. Except for the child who is deaf, there is little evidence concerning the recessive nature of the ailments. This listing may, however, in conjunction with others, prove useful in establishing the role of recessive inheritance of certain of these ailments. Even in the case of the deaf child there is the possibility that the other conditions that he displays may be pleiotropic effects of the gene responsible for the deafness.

The similarity of available medical treatment may be investigated by a determination of the frequency of more routine medical procedures. Among the living consanguineous children, 76 have had tonsillectomies, 3 have had appendectomies, and 10 others have had both of these operations (40, 2, and 5 per cent, respectively). Among the controls, these values are 69, 6, and 7 (42, 4, and 4 per cent, respectively). These operations have been slightly more frequent among the controls. The differences are not statistically significant. The only unusual occurrence among these cases is that a (living) female in family 11 (see table 5) is noted as having had double pneumonia after her appendectomy at age 7 weeks.

When the incidence of broken bones was used as an impartial index of accidental occurrences, inquiry revealed that 13 of the consanguineous children have each had one fracture; nine of the control children have had a single fracture and one additional control has had three fractures. Thus, children with broken bones occur in almost the exact ratio as the numbers of the two classes of children. No case of unusual bone fragility has been observed.

TABLE 6. AILMENTS AND ABNORMALITIES OF CONSANGUINEOUS LIVING CHILDREN

	M	F	Complaint
	1		Hydrocephaly (age 3, not expected to survive longer).
	1		Deaf. Also has hernia; an undescended testis.
	1		Blind (infectious etiology?)
	1		Poor heart and respiratory function (in a nursing home).
	1		Mentally retarded.
	2		Cerebral palsy and leg abnormalities (brothers, there are indications that Rh incompatability was responsible).
	1		Rheumatic fever (severe case with frequent hospitalization).
	1		Bilaterial hernia.
		1	Hernia.
		1	Cleft palate.
	1		Defective hearing.
	1		Enlarged thymus (fed intravenously for a period).
	1		Pyloric spasm (?)
	1		Pityriasis rubra pilaris.
	1		Osgood-Schlatter disease.
		1	Nervous eczema (neurodermatitis?).
		1	Partial removal of a kidney.
	1		Convulsions in infancy.
	1		Mastoid operation.
		1	Rheumatic fever.
	4	3	Pneumonia (two males have also had convulsions).
	2		Polio (one child now has an abnormal spinal curvature).
	1		Spinal meningitis.
Total	23	8	

TABLE 7. AILMENTS AND ABNORMALITIES OF CONTROL LIVING CHILDREN

	M	F	Complaint
	1		Congenital pilonidal cyst.
	1		Gall bladder disease.
		1	Cleft palate.
		1	Congenital cataract.
	2		Hernia.
	1		"Cysts on chest."
	1		"Gland trouble in the neck."
		1	Nervous eczema (neurodermatitis?).
		1	Defective eye muscle.
		1	Psoriasis.
	2		Pneumonia (one of these children was affected twice).
		1	Mastoid operation.
	1		Polio.
		1	Spinal meningitis.
Total	9	7	

With minor exceptions, schooling is essentially a function of age up to about the age of 16. Official school records have not been obtained for these children. Of the 21 consanguineous children who have reached the age of 19 (which is a convenient age for ascertaining the likelihood that higher education will be pursued), five have

taken some college work. Of the 36 control children aged 19 or greater, 15 have had some college work. The difference between the two groups is not significant ($\chi^2 = 1.15$, 1 d.f., $P > .05$).

A number of the older children are married, but no analysis of the number of their offspring has been made. Few of them have been married any length of time.

The three families which have a greater degree of consanguinity than that of first cousins have not contributed to the abnormalities observed among the consanguineous children. The aunt-nephew marriage has been sterile. The three children of the double first cousins are all less than six years of age and have not had any recorded medical treatment. The uncle-niece family has had one miscarriage and four live-born children. Their only recorded medical treatment is that three of the children have had tonsillectomies.

DISCUSSION

In this comparison between the consanguineous and control groups the major questions are the fertility of these marriages, the viability of the fetuses, and the viability and health of the children. Some doubt exists about the possibility of a mechanism that could cause the sterility of a consanguineous couple. Common heterozygosity for a large number of early-acting recessive lethal genes would easily account for this phenomenon, but this would suggest that most consanguineous couples should have difficulties in conceiving. On the contrary, the median times to first and second births are less than those of the controls. Schull (1958) has investigated the time to first birth for consanguineous couples in a large Japanese sample and he too finds little or no effect on the time to first birth. Nevertheless, our data suggest that the frequency of sterility may be higher among consanguineous couples. Also Remlinger and Coen (1947) have reported a high frequency of sterility in closely consanguineous marriages among Moroccan Jews, and Sutter and Tabah (1952) found a slightly elevated frequency of sterility among the consanguineous couples in their study of French Catholics. Thus, the existence of early-acting recessive lethal genes in the population, as deduced from observations on sterility and time to first birth, is still open to question.

With respect to miscarriages and stillbirths, the numbers observed in the two groups are so similar that there seems to be little, if any, effect of consanguinity on these conditions. Thus, for all stages from conception to live birth, there may not be any effect of consanguinity. This fact is important for the understanding of the time of action of deleterious genes.

The relatively equal viability up to the time of live birth soon changes for the worse among the consanguineous children. It is a frequent observation that some types of abnormality are increased among the children of consanguineous marriages. The relative frequency of abnormality that has appeared thus far in this study has been high. The death rate during childhood has already exceeded eight per cent, which is very high for the population of the Chicago area for the period of time under consideration. Also, the frequency of serious abnormalities among the living children is well above the usual level for this area. On the other hand, the controls

appear to reflect the level of death and abnormality expected in the general population.

A number of papers have recently discussed the calculation of the number of abnormal recessive genes in an average person using data derived from the study of consanguineous marriages. Slatis (1954) derived a formula that takes into account the small size of families, so that a correction is made for the chance that a couple will have a recessive gene in common but will not show it among their progeny. He derived a value of eight as the average number of abnormal recessive genes carried heterozygously per person, but the data were admittedly biased in favor of a high rate. Böök (1957) has used a different method, which is based on the same principles, and arrived at an estimate of three detrimental recessive genes per person in a North Swedish population. Böök's method makes two unusual assumptions: (1) that among families showing at least one recessive mutant, no further information is derived from the family size or the number of mutants segregating, and (2) that miscarriages and stillborn children are normal.

By subtracting the wasted pregnancies and by using Slatis' formula, which takes into account the number of separate mutant genes observed in each family, one finds that Böök's data give an average value of 5.32 detrimental mutant genes per person. Penrose (1957) has also analyzed Böök's data, correcting them to eliminate the miscarriages and stillbirths. His method is satisfactory in large samples, though it will be less accurate than Slatis' method in these small samples. Penrose suggested that the number of deleterious genes observed among the children of first cousins would reflect $\frac{1}{16}$ of the number present heterozygously in the average common great-grandparent, but this value should be $\frac{1}{32}$. Therefore, Penrose's calculation of 2.94 deleterious genes (16 times the frequency of individuals homozygous for a deleterious gene) should be doubled to 5.88, which is reasonably close to the value calculated by Slatis' method. These values for Böök's data are only about one standard error below Slatis' calculation of 8.0 ± 2.6.

Morton, Crow and Muller (1956) have advanced the concept of lethal equivalents, which is more sophisticated than the concepts of simple recessivity previously employed. Their estimates of the number of lethal equivalents are derived by assuming that the difference in death rate between the consanguineous and control populations is an expression of lethal genes of various degrees of penetrance. In data such as ours in which the observations are (essentially) limited to controls and a single type of consanguinity, simple mathematical procedures may be used. As observed above, for data on first cousins, the homozygous recessive genes reflect $\frac{1}{32}$ of those present in an average common ancestor. Therefore, the number of lethal equivalents carried by an average individual may be found by multiplying by 32 the difference: (frequency of death among the consanguineous children) − (frequency of death among the control children). For our data, this method is similar to that of Penrose, but it includes a correction for the mortality observed among the controls. It yields a measure of the sum of the number of rare lethal and semilethal genes times their penetrances, rather than of the number of loci at which a lethal gene occurs.

It should be stressed that the observed differences in miscarriage and stillbirth

rates in our data are far too small to have any importance attached to them. They are, however, in the direction expected on the theory that they are caused by recessive lethals, and a value representing the indicated number of lethal equivalents can be calculated. The controls, having lost .1289 of their pregnancies through miscarriage, show .0163 fewer losses than the .1452 shown by the consanguineous group. Multiplied by 32, the indicated number of lethal equivalents in the average person that would act in this period of development is .52. Stillbirths show a difference of .0024, or .08 lethal equivalent. Neonatal deaths (deaths within the first month of life, which is the definition used by Sutter and Tabah, 1952, whose data are analyzed by Morton, Crow and Muller) show a difference of .0011, which indicates the action of .03 lethal equivalent. This total of .11 for the lethal equivalents for stillbirths and neonatal deaths is only a small fraction of the number calculated by Morton, Crow and Muller, and even if part of the miscarriage rate should be included, it would still be extremely low. The reader is referred to the discussion by Morton, Crow and Muller for remarks pertinent to the "relaxation of selection under modern conditions" which probably is indicated by our low perinatal mortality. Infantile and juvenile deaths occurred in our study to .0061 of the control children and .0634 of the consanguineous children, which gives a difference of .0573 and an indication of 1.83 lethal equivalents. The total number of lethal equivalents from early miscarriage through the juvenile period is thus 2.46.

Parallel with the concept of lethal equivalents is that of abnormal equivalents, the number of fully penetrant genes that would give the observed increase in abnormalities. The abnormalities listed in tables 6 and 7 occur in 31/192, or .1615 of the consanguineous children and 16/163, or .0982 of the control children. If due to the effect of consanguinity, this difference, .0633, indicates the presence of 2.03 abnormal gene equivalents.

As seen in table 8, the consanguineous families and the control families appear to differ because of the action of a total of 4.49 detrimental gene equivalents. These were carried by the average great-grandparent of the consanguineous children and, subject to the errors inherent in our methods, this would approximate the average number carried by the members of our contemporary society. The failure to observe all of the children through the entire juvenile period could be construed as indicating that this value is, to a slight extent, an underestimate. The relaxation of selection

TABLE 8. LETHAL AND ABNORMAL EQUIVALENTS AT VARIOUS STAGES IN THE LIVES OF CONSANGUINEOUS AND CONTROL CHILDREN

Stage	Consanguineous			Control			Difference	Difference × 32 = no. of equivalents
	Affected	Total	Frequency	Affected	Total	Frequency		
Miscarriage	36	248	.1452	25	194	.1289	.0163	.52
Stillbirth	3	212	.0142	2	169	.0118	.0024	.08
Neonatal death	4	209	.0191	3	167	.0180	.0011	.03
Infantile and juvenile death	13	205	.0634	1	164	.0061	.0573	1.83
Abnormality	31	192	.1615	16	163	.0982	.0633	2.03
Total								4.49

to which we have referred would suggest that this difference was even greater only a generation or two ago. It should be noted that because of incomplete penetrance the estimate of the number of lethal equivalents plus abnormal equivalents will give a smaller value than the actual number of loci involved.

It has been hoped that the results of this study could be used to estimate the added risk of harm to the children in a consanguineous marriage. The *indicated* increased probability of loss through stillbirth is .0024, through neonatal death is .0011, and through infantile and juvenile death is .0573. The added risk of sickness or abnormality is indicated to be .0633. These values suggest that, in the society studied, there is an added risk such that an additional 12 per cent of the children of consanguineous couples will be affected over the percent affected among outbred children. The controls have shown a very low rate of death, which sociologically is one of the most severe of these conditions, and the indication is that the death of children is three times as great among consanguineous families as among controls, i.e., 17 of 209 consanguineous children as compared to 4 of 167 control children. The rate of all abnormalities, as defined by tables 6 and 7, is less than twice as great among the consanguineous children, but if only major abnormalities are considered, the added risk of consanguinity is exceedingly great, i.e., 8 of 192 living consanguineous children have had serious abnormalities, whereas 0 of 163 living control children have suffered serious abnormalities.

SUMMARY

A study has been made of 109 consanguineous marriages in the Chicago area, of 83 control marriages, and of a few aspects of 133 other control marriages. The consanguineous marriages give some evidence for a greater frequency of sterility and of childhood death and childhood abnormality. The loss of children through miscarriage and stillbirth was not significantly higher, and there is no evidence that rare recessive lethal genes cause the loss of newly fertilized zygotes. Subject to the errors inherent in our methods, the indicated number of lethal equivalents per person is 2.46, and 2.03 abnormal equivalents are also found. Thus, the average person may be carrying the equivalent of 4.49 fully penetrant genes which cause detrimental effects in a modern American population. To some extent these values are underestimates for the population studied, and the ancestors of this population under more primitive conditions probably expressed the lethality and abnormality of many additional genes. The rate of death among the consanguineous children is three times that of the controls and their rate of abnormality is also greatly increased, the amount of the increase being dependent upon the definition of abnormality.

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The Bearing of a Complex-Locus in Drosophila on the Interpretation of the Rh Series[1]

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TWO MAJOR HYPOTHESES have been offered concerning the genetics of the Rh factors, one by A. S. Wiener (see review, 1954) and the other by R. A. Fisher and R. R. Race (see Race and Sanger, 1954). In Wiener's concept the various mutants of the Rh system are multiple alleles of a single gene. The Fisher-Race hypothesis assumes that the three major antigens, C, D, and E, are the separate products of three closely linked genes symbolized, in their presumed map order, by the letters D, C, and E. These three genes with their corresponding alleles would form a series of eight possible genotypes for any chromosome containing the Rh region.

Attempts to prove either theory directly have been unsuccessful because of the difficulty involved in obtaining the large number of pedigrees which would be necessary to test a close-linkage theory. Proponents of each interpretation have tried to use population analysis for contradiction or support of the close-linkage theory, which would require equilibrium values in long panmictic populations but a relative rarity of certain crossover types unless the panmixia has been exceedingly ancient; but this study has been hampered by inadequate knowledge of the history of the populations in primitive times.

Supporters of the Fisher-Race theory maintain, in addition, that the adoption of their close-linkage theory would enable the nomenclature of a CDE type to be easily acquired by technicians. On the other hand, according to advocates of Wiener's theory, such a system would result in over-simplifications and possible misclassifications for such important aspects of the Rh field as forensic medicine. Each side has hoped to have its system considered as an international one which would obviate the learning of two systems.

The problem of nomenclature is important not only in the Rh controversy but also in the study of pseudoallelism itself. At present no international agreement has been reached and each investigator has used his own terminology for his particular studies. It is to be hoped that an international agreement will be reached once

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geneticists have come to a general agreement concerning the problems of allelism, pseudoallelism, and "complementarity" (non-allelism). It would be useful for such systems to be applicable to man as well as to laboratory organisms since this would reduce the resulting confusion that arises out of shifting from one system to another.

An interpretation of the Rh system which could incorporate aspects of both the multiple allele and close-linkage hypotheses, and which seems to eliminate many of the difficulties in the controversy, is suggested by an analysis of a complex locus that has been investigated in *Drosophila melanogaster* (see Muller, 1919, 1923, 1939; Fogel, 1949; Muller, Meyer and Carlson, 1955; Carlson, in press). The genetic region in question, that of the dumpy series of mutants, is located in the second chromosome and has been localized at about 13.0 on the standard linkage map proposed by Bridges (1935, 1938). The alleles of this dumpy region may exhibit any of three major recessive mutant characteristics, singly or in combination, giving a total of eight types—seven mutant and one wild type or normal (+). These three characteristics are designated *o*, *v*, and *l*, respectively, for the following effects: (o) a reduction in wing size, with characteristic *oblique* truncation of the wing tips; (v) the presence of either abnormal growths or pigmented pits on the thorax with whorls of microchaetae and bristles, collectively called *vortex*; and (l) a homozygous *lethal* effect.

In the history of the dumpy locus the mutants were given unrelated names before it was found (Muller, 1919) that they were members of a multiple allelic series. For this reason the original terminology had no uniformity or interconvertible symbolism. The original terms, such as thoraxate (dp^{tx}), lopped (dp^{L}), and truncate (dp^{T}) have recently been discontinued in favor of designations of the combinations of phenotypic effects (designated *'lv*, *'ol*, and *'olv*, respectively). To simplify the nomenclature, the base (dp, here) has been omitted and an apostrophe substituted to designate this omission. This has permitted the superscripts that were used in the intermediate period of the investigation (when the members were designated dp^{o}, dp^{olv}, etc.) to be put on the base line (e.g. *'o*, *'olv*, etc.).

All of the numerous members of this series thus far dealt with are capable of being represented in terms of the given pleiotropic effects (e.g. as *'o*, *'v*, *'l*, *'ol*, *'lv*, *'ov*, *'olv*, '+). If mutations occur in the same sublocus region, the members are designated with an additional superscript (e.g. $'ov^{1}$, $'ov^{n}$, and $'ov^{51f}$). Since, ordinarily, only those functional elements are manifested in an individual which are common to both homologous chromosomes, it is possible to tell at a glance what the phenotype would be from the designation of genotypes present (e.g. *'ol/'ov* is (o), *'o/'lv* is (+), *'ol/'lv* is lethal, and *'olv/'ov* is (ov). By enclosing the phenotype in parentheses and omitting the apostrophe it is possible to use the same functional symbol for the phenotype as well as the genotype without confusion. However, as will be illustrated later, this system does not account for all the phenotypic subtleties, both qualitative and quantitative.

The first interpretation suggested for this system by the author in his investigation of the region was based on the Fisher-Race CDE model. Since there were three effects, and eight possible phenotypic combinations which could be expressed, an attempt was made to separate the appropriate alleles from one another. Preliminary

work showed *'o* to be to the left of *'v*, *'ol* to the left of *'v*, and *'o* to the left of *'lv*. This suggested that the order of the three subloci should be *o-l-v*.

Attempts were then made to demonstrate a separable lethal situated between the *'o* and *'v*, using two double mutants obtained by recombination, namely *'o'lv* and *'ol'v* (both having the olv effects) as well as, thirdly, an *'olv* "point mutation" which had arisen from a wild-type second chromosome. However, these three members, in heterozygous compound with the wild type (+), showed no evidence of a separation of the lethal element from the allele with which it had been originally associated. Thus *'o'lv*/+ gave *'o* and *'lv* crossovers only; *'ol'v*/+ gave *'ol* and *'v* crossovers only; and *'olv*/+ gave no recombinants. Furthermore, differences in the frequency of recombination, for those compounds which were able to yield crossovers, suggested that *'lv* was to the left of *'v*. Tests of these two alleles in compound with each other were then made, and recombination was obtained between them. At the same time, the predicted localization of these two subloci was verified by the use of outside markers. These outside markers, echinoid (11.0) and clot (16.5) covered a total of 5.5 map units and hence they minimized the possibility of double crossovers occurring in this region.

Continued investigation of the various members of this region has indicated the following localizations for the series:

'l	*'ol*	*'olv*	*'o*	*'lv*	*'ov*	*'v*	
0.03	0.015	0.015	0.011	0.018	0.04		map units

The four rightmost members, *'o*, *'lv*, *'ov*, *'v* have been directly mapped by means of recombinations occurring in the intervals between the adjacent members tested, with the sign of their positions with respect to one another determined by the two outside markers. The four leftmost members *'l*, *'ol*, *'olv*, *'o* have been assigned their map locations more tentatively, on the basis of their differences in crossover rates with the same standard reference, *'ov*.

About 480,000 flies were counted in all the crossover tests combined to obtain somewhat more than one hundred verified crossovers which established the map relations illustrated above. (For a full account of the details of this analysis, see Carlson, "Allelism, complementarity, and pseudoallelism at the dumpy locus in *D. melanogaster*," submitted to *Genetics*).

The dumpy region occupies about 0.13 map units (0.13% crossingover) with the most closely linked pair, *'o* and *'lv*, about 0.01 map units apart. Because of the large number of mutational sites within the region, and because of the functional relatedness of these mutants, the whole region is considered a complex but single functional unit, analogous to the *cistrons* proposed by Benzer (1955) for Bacteriophage. It differs however in certain features. One of these shows that not all compounds of mutants in this series give a mutant expression in the *trans* condition. Because the cistron was defined in terms of the *cis-trans* differences observed in certain genetic regions, its usage here would be misleading; hence the term "gene" is retained for the dumpy region. Another feature suggests an internal discontinuity between mutational sites within the locus-complex. It is inferred that if such a functional unit should be separated into fragments by breakage and subsequent rearrangement, the region would be incapable of normal functioning. If, however, localized

lesions of a very small size (comprising one tenth or less of the entire gene) were to occur, then the altered gene might function in a way which would reflect the type of damage the gene itself had sustained; that is, the presence of a lesion would not necessarily inactivate the entire gene.

That mutants of a genetic region can represent alterations of only some of the properties of the molecule it produces, has been demonstrated on a chemical level for the tryptophan synthetase molecule in *Neurospora* by Yanofsky and Bonner, 1955. This molecule is unable to function normally as an enzyme when certain mutations occur at the locus responsible for its production, but its antigenic activity is nevertheless not impaired. Other known mutations of the locus result in the loss of the antigenic activity as well. Similarly, minor changes may occur in hemaglobin molecules and these may result in severe mutant expressions (such as sickle cell anemia). In the latter case the lesions in the molecule are so slight that the chemical properties of the hemoglobin are for the most part unaffected. Indeed, it has only been with very refined techniques that these chemical differences have been detected and analyzed (Itano 1957, Ingram 1958).

It is entirely compatible with present knowledge for a multiple allelic series to have crossing over occur within the functional region which expresses this series. The recombination establishes, in a preliminary way, where the lesion in the gene has occurred in terms of the map distance for this region. Thus the analogy of the dumpy series to the Rh series would have the following advantages: (a) it would bring the two theories presently in use more up-to-date with what has been found in recent years concerning pseudoalleles and gene structure; (b) it would enable the retention, for mnemonic purposes, of a modified functional CDE terminology, as has been the case for the dumpy series, but without loss of the rigorous designation of the actual genotype, which, in the case of the Rh series only Wiener's system presently takes into consideration; (c) it would offer more opportunities for further investigation and should enable finer immunogenetic distinctions to be made; and (d) the refined nomenclature and resulting immunogenetic details should lead to a more exact Rh classification and benefit applications in forensic medicine.

There are many difficulties to demonstrating crossing over within the Rh region in man. First, pedigree analysis is necessary and this introduces errors resulting from illegitimacy as well as errors in typing. Second, putative genotypes for the Rh series are based on observed phenotypes in usually heterozygous individuals. Third, very large numbers of pedigrees must be used for a critical evaluation.

Fortunately there are some checks on illegitimacy and often the data from the mother and her children alone can be used. But the problem of phenotype is not easily solved. Geneticists have long realized that phenotypic designations are not identical with genotypic designations for many cases. Thus it is easy for two mutants of the same or similar homozygous expression to be given the same symbol for their phenotype as for their genotype (e.g. f^x and f^3 have an (f) phenotype). Difficulties begin to arise when white, *w*, and apricot, w^a, are mutually heterozygous. The eye color is intermediate in shade between the two. How should this be designated symbolically? Or consider the mutants Star, *S*, and asteroid, *ast*. Both reduce the size of the eye slightly and produce a roughening of its texture. But in the *trans* compound,

S/ast, the eyes are reduced to narrow slits and a new characteristic—missing wing veins—is present! How could this be phenotypically symbolized? In both the dumpy series and the Rh series, fortunately, the functional elements expressed and the genotypic designations for them are similar and for this reason they are more akin to the forked example cited.

The problem of large populations is even more formidable. In the dumpy series the amount of crossing over in the various series ranged between 0.13 per cent (1/800) and 0.011 per cent (1/9000) for those combinations which were able to yield verified crossovers. If a similar situation existed in the Rh series, the number of individuals tested would have to be raised much higher because of the relative rarity of finding, in random samples from panmictic populations, homologous chromosomes containing two Rh positive genotypes which were not homozygous for the identical genotype. Race and Sanger (1954) estimate that an individual investigator's lifetime would be scarcely long enough to detect the occurrence of such a case of crossing over. Furthermore, any such instances reported are subject to other interpretations of forward and reverse mutations in the absence of linked genetic markers on either side of the Rh region.

A major problem for genotypic identification is involved with the phenotypic expressions of the various mutants, alone and in combination, of the dumpy series. On the over-simplified o-l-v model, there are thirty-six possible genotypes, seven of which are able to show viable (o) phenotypes and seven with viable (v) phenotypes. But in both cases the (o) and (v) expressions are, for the most part, distinguishable from one another quantitatively and qualitatively, in terms of how much the wing is reduced as well as its shape, and of how intense the vortices, pigmentation, or mounds appear on the thorax. The reasons for such differences reside in the complexity of the genetic material itself, and its extremely delicate relation to all the developmental processes. All of these mutants are lesions at different sites within the dumpy gene and the altered complex in each case is different in its chemical structure. The entire region is believed to be functioning at three separate periods of development: the oblique effect at 13–14 hours after pupation, the vortex effect about 6–10 hours after pupation, and the lethal effect before pupation commences (see Blanc and Child, 1937 and Carlson, in press). This is one reason why the *trans* compound bearing two genes containing one of the pleiotropic effects in common could result in a phenotype different from the homozygote for either mutant alone, where this type of interaction between dissimilar genes at a specific stage of development would not be present.

The difference between two such mutants in the *trans* compound (showing a mutant expression) and the same genes after crossing over between the subloci of the region has occurred (giving a double mutant gene and an intact gene, known as the *cis* form, resulting in a non-mutant expression) has been called positional pseudoallelism or the Lewis effect, after its discoverer (see Lewis 1950). This very difference between *cis* and *trans* arrangements of the Rh antigen elements has been reported by Cameron *et al* in 1954, using the pairs *CdE/cde* and *Cde/cdE* as one case of a *cis-trans* difference, and the pairs *CDE/cDe* and *CDe/cDE* as another case. In both instances, if the *C* and *E* elements are in a *cis* alignment, the C antigen is depressed, but not the E antigen. The reverse occurs when *C* and *E* are in a *trans* alignment. Notice, then,

the striking similarity here between the Rh and the dumpy series. Thus in the compound *'ol/'ov* the wing size is reduced, with viability and fertility relatively unaffected. But in the compound *'o/'olv* (which contains elements for the same phenotypic effects as the former compound) the wing is even more reduced, and the reduction in body size and leg size considerably weakens the chances of these flies to mate. Furthermore, even when mating is successful, the fertility is reduced. The separability of these two phenotypes is exact.

Similarly, the compound *'lv/'ov* shows a very disturbed thorax, with prominent mounds protruding through the whorled bristles and microchaetae. Viability of this compound is normal, or nearly so. But the heterozygote *'v/'olv*, which also contains elements for the same phenotypic effects, does not show these protrusions; instead, the thorax is marked by four pigmented pits. Such flies are relatively inviable and occur with much less frequency than do those of the *'lv/'ov* composition when attempts are made to produce them.

It is important to bear in mind that these types of differences are not true *cis-trans* differences, at least not in the sense for which Lewis originally applied the term. They would represent such *cis-trans* differences if the model with just one sublocus for each of the three effects had been valid for the dumpy series. Nevertheless, they illustrate the degrees to which the functional or pleiotropic expressions of any single mutant can differ, depending on where its lesion in the gene has occurred, just what lesion has occurred in that gene, and with what other mutant it interacts in the *trans* compound.

True *cis-trans* differences are present in the dumpy series (e.g. *'ov/'lv* shows the prominent vortex characteristics described above, but the *cis* counterpart *'lv'ov/+* is wild type or normal in phenotype). Whether such *cis-trans* arrangements can be detected in the Rh series is not yet known. But if, for example, *'CDe* and *'cdE* represent primary mutants each of which involves but one sublocus, and if they have by a subsequent crossing over formed the *cis* combination *'CDe'cdE*, then the *cis* heterozygote, *'CDe'cdE/+* might show a quantitative or even a qualitative difference in its antigen activity for the anti-C,-D,-E,-c, and -e serums available, not only from the *trans* counterpart *'CDe/'cdE*, but from the similar combination but different permutation *'CDE/'cde*, which contains elements for the same antigenic expressions. This type of difference might explain some of the reported alleles of the *C* and *D* types in the Fisher-Race system (e.g. C^w and D^u show peculiar antigenic reactions with anti-C and anti-D serums suggesting to some investigators that a modifier is present and to other investigators that quantitative as well as qualitative differences of an allelic nature are present. See Race and Sanger, 1954 for review).

In the dumpy region the double lesion genes which arise from recombination may often exert more of an effect on one than on another of a group of pleiotropic characters. Thus *'o'v/'o'v* shows a more intense effect on the v character than on the o character. It therefore requires considerable caution, in the cases of multiple allelic series, to state with assurance whether it is a mutant at one sublocus, or an intensification (by the type of recombination mentioned here), or a modification (by suppressor or enhancer mutations occurring nearby or far away) that is the basis of a

newly observed phenotype (such as D^u or C^w). Only careful genetic analysis can establish the proper diagnosis (See, for example, Ceppellini *et al.*, 1955.) In man the geneticist is handicapped by the paucity of useful linkages, the difficulty of long generations, the limited number of appropriate pedigrees, the small number per family, and the inability to control the crosses. In the Rh field however, he has a tool —the immunological reactions—which should enable him to detect much subtler differences than the visible criteria alone which geneticists, for the most part, employ in their laboratory organisms. Perhaps it is this refined level of immunology which may solve the complicated genetic changes in the Rh series.

It should be emphasized that a retention of the *CDE* nomenclature does not so much require a change in its present form as in its interpretation. If the individual genotypes (e.g. *'cDe*, *'cdE*, *'cDE*, *'cde*, etc.) are considered point mutations (as in the dumpy series) rather than combinations of three separate loci, then the types of oversimplifications discussed for the dumpy series could be avoided. Thus, if *'CDE* is a point mutation (like *'olv*), it cannot be resolved into simpler functional components. However, the possible types of recombinant mutants (*'o'lv*, *'ol'v*, *'l'o'v*, *'ol'ov*, *'lv'ov*, etc.) which express the same phenotypic elements are very numerous although their occurrence is a rare event. There is no way at present to rule out a similar profusion of rare genotypes for the *CcDEe* phenotype (*'CDe'cdE*, *'cDE'Cde*, *'Cde'cDe'cdE*, *'CDe'cDE*, *'cDe'CDE*, etc.). Because the combinations possible for these rare types of compound mutants are large and because so little is known of their behaviour in Drosophila or the Rh series, it seems to be a more cautious policy when using a functional symbolism to designate the members in a way that represents them as point mutations until they are shown experimentally to be of a compound nature. This can be done for the Rh as well as for the dumpy series by using the functional symbol with its base (e.g. rh^{cde}, rh^{cDE}, etc.) or by using the apostrophe to indicate its membership as a mutant member of a complex locus (e.g. *'cde*, *'cDE*, etc.). Note that the dumpy series could have used the old nomenclature (dp^{tz}, dp^{T}, etc.) and a three-locus nomenclature (*ol*, *olv*, etc.) without contradiction until compound mutants containing the same phenotypic elements were synthesized (e.g. *'lv'ov*) which ruled out a "one-gene:one function" interpretation and which ruled out absolute linkage without crossing over. Note, too, that in both cases the original non-functional symbolism is perfectly accurate and its replacement can only be justified by the simplicity of comprehending rapidly the functional elements expressed by these series.

In conclusion the author wishes to emphasize the point that the Rh series is not yet a genetically established case of multiple alleles in the strict sense, or of three closely linked loci, or of a gene with several mutable sites. It is hoped, however, that the suggestive similarities between the dumpy and the Rh series will point out certain problems concerning the means by which these three interpretations may be tested. The possibility of a single gene with several mutable sites has the virtue of including both of the apparently mutually exclusive claims (recombination as opposed to a single functional molecule whose alleles represent different changes within it) between which the other two theories have attempted to choose. It provides, in addition, a model for a possible revision of the Rh nomenclature without sacrificing the simplicity

of the CDE terminology or the exactitude of genotypic designation which the Wiener system provides. It also points out the enormous complexity of the genetic material, both in its structural and functional aspects, which might be overlooked by adopting an over-simplified model of gene structure and action.

SUMMARY

A possible alternative to the interpretation of multiple Rh alleles (A. S. Wiener) and closely-linked but essentially independent CDE loci (R. A. Fisher and R. R. Race) is presented.

The alternative interpretation is based on analogy with a genetic region in *Drosophila melanogaster* which has eight different phenotypic combinations (consisting of seven mutant subloci and one normal locus), which form all of the possible combinations of the three different pairs of effects in this series (without taking into account different genetically conditioned degrees of these effects).

All of the mutant members of this series can be mapped within the region by recombination. However, a given type of effect is not confined to a given sublocus, and a given sublocus is not confined to a given type of effect. Nevertheless the region acts for the most part as a functionally single gene.

The application of the finding of this series to the Rh system suggests that the major differences between the two existing hypotheses are reconcilable.

Implications of this interpretation for more refined immunological tests and for forensic medicine are discussed.

A possible compromise of the nomenclature controversy, which would retain the CDE notation as an indication of the phenotype, but which does not make unjustified genotypic assumptions, is offered for consideration.

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An Rh Blood Factor, rh_i (Ce), and Its Relationship to hr (ce)

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MOURANT (1957), when introducing a review on the current state of knowledge and codification of the Rh system, stated, "It is . . . not to be expected that it will be easy, or even possible, to devise a notation which will cover the serological and genetical facts completely and at the same time simply." Recognizing the inherent complexities as well as the limitations of available data, the present report employs terms of A. S. Wiener (1954[a], 1954[b], 1958) and A. E. Mourant (1957) to describe data pertaining to an Rh antiserum, Ba, and its reactions with a common Rh blood factor that has not thus far been designated.

THE BA SERUM

The donor of the serum studied, Mrs. Ba, was not available for testing, but her blood type was known to be O Rh_2Rh_2 (ccDEE). The serum was kindly supplied by Certified Blood Donor Service, Inc., Jamaica, N. Y. Mrs. Ba, from the meager history, was probably immunized by multiple blood transfusions and possibly by earlier pregnancies.

The *native* Ba serum was found to react with all group O test cells except those negative for the Rh factor, **hr″** (e). The antibody activity was best demonstrated by enzyme technic, and ficin was found to be superior to trypsin for treatment of the test cells. Absorption with A and B red cells of type Rh_2Rh_2 (ccDEE) did not affect the Rh antibody activity and permitted tests with red cells of any ABO group.

The titers of the Ba serum with test cells of different Rh type were found to be unequal. Test cells of type Rh_0 and rh (C−e+) were not agglutinated as strongly as test cells of type Rh_1 and rh′ (C+e+). These reactions are summarized in table 1.

The need for a more extensive investigation arose after observations that this serum failed to agglutinate a blood of type Rh_zRh_z (CCDEE) (kindly supplied by Dr. Eloise Giblett, Seattle, Wash.) and another of type Rh_zRh_2 (CcDEE). Absorption of the Ba serum with Rh_zRh_z and Rh_zRh_2 red cells failed to alter the antibody activity, and eluates from the absorbing red cells were inactive. These results proved that distinctions noted in table 1, could not have been due to the presence of anti-**rh′**(C), because anti-**rh′**(C) reacts with red cells of types Rh_zRh_z and Rh_zRh_2. The problem was to explain the mechanism of the preferential reactions noted with Rh_1 and rh′ (C+e+) test cells.

Separate anti-**hr**(f) could not be demonstrated in the Ba serum. After five absorp-

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TABLE 1. REACTIONS OF NATIVE Ba SERUM

Phenotype of Test Cell	Titer Value by Various Technics				
	Saline	Trypsin	Ficin	Albumin	Coombs
Rh_0 or rh (cceeff)	0	2	4	0	0
Rh_1 or rh′ (Cceef or CCee)	0	16	128	8	1
Rh_2Rh_2 (ccEE)	0	0	0	0	0

TABLE 2. ABSORPTION CHARACTERISTICS OF THE Ba SERUM

Phenotype of Absorbing Blood		Number of Absorptions	Ficin Titer Against:			
			(ccee)		(Ccee)	
			Rh_0	rh	Rh_1	rh′
Rh_2Rh_2	(ccDEE)	× 10	2	2	32	32
Rh_1Rh_1	(CCDee)	× 5	0	0	0	0
>Rh_0, rh, Rh_2rh	(cceef)	>× 4	>0	0	16	16
		× 6	0	0	10	10
		× 10	0	0	5	5
rh′rh	(Ccdeef)	× 5	0	0	0	0
rh_yrh	(CcdEef)	× 5	0	0	12	12

> Reagent used in this investigation.

tions with ½ volume washed and packed Rh_1Rh_1 (CCDee) red cells, each absorption incubated 30 minutes at 37°C., no residual antibody activity could be detected.

On the other hand, following repeated absorption with either Rh_0, rh, or Rh_2rh (C−e+f+) red cells, anti-**hr**″(e) and/or possible anti-**hr**(f) was removed leaving antibody activity demonstrable with test cells of types Rh_1 and rh′ (C+e+), but not with test cells of types Rh_0, rh, or Rh_2 (C−e+).

Strikingly similar results were obtained, however, by substituting rh_yrh (CcdEef) and Rh_zrh (CcDEef) as absorbing red cells. This showed that the presence of the **rh**′(C) factor in the absorbing blood did not affect the result as long as the **rh**′(C) factor was derived from products of R^z or r^y rather than from products of R^1 or r' alleles.

Continued absorption was found to reduce antibody activity beyond the mere dilution effect noted in parallel treatment of the Ba serum with Rh_2Rh_2 (ccDEE) red cells. Although this suggested that at least some of the residual antibody activity cross-reacted with **hr**″(e) and/or **hr**(f), a satisfactory reagent was obtained after four absorptions of the native serum with any red cells lacking a product of R^1 or r' alleles. This reagent agglutinated Rh_1 and rh′ test cells very well, but failed to agglutinate test cells of types rh, Rh_0, Rh_2, rh_yrh, or Rh_zrh. The absorption characteristics of the native Ba serum are summarized in table 2.

If the absorbed Ba serum was not to be considered to have anti-**rh**′(C) specificity because it failed to react with red cells containing **rh**′(C) produced by R^z or r^y alleles, another term had to be devised. The blood factor detected by the Ba serum occurs in products of the established alleles, R^1 and r'. Substituting "i" for "one" and for "prime", the term **rh**$_i$ was evolved (Wiener 1958). In CDE terms, C and e, as well as the factor detected by the Ba serum, are produced by the established alleles, R^1 and

r'. Since therefore the Ba factor has been found when and only when an allele producing both C and e was present, the Ba factor might be termed Ce.

SPECIFICITY OF ANTI-$\mathbf{rh_i}$(Ce) REAGENT

Anti-$\mathbf{rh_i}$(Ce) was tested in parallel with several anti-$\mathbf{rh'}$(C) and anti-$\mathbf{hr''}$(e) sera. "Pure" anti-$\mathbf{rh'}$(C) was available from Rh− and Rh+ donors, as well as the more

TABLE 3. REACTIONS OF ANTI-$\mathbf{rh_i}$(Ce) WITH VARIOUS Rh GENOTYPES

Genotypes of Individuals Used for Test Cells		$\mathbf{rh_i}$ Ce	rh′ C	$\mathbf{Rh_0}$ D	rh″ E	hr′ c	hr″ e	hr f	$\mathbf{hr^v}$ V	$\mathbf{rh^{w1}}$ C^w	$\mathbf{rh^x}$ C^x
rr	*cde/cde*	−	−	−	−	+	+	+	−	−	−
rr^v	*cde/cdeV*	−	−	−	−	+	+	+	+	−	−
r^vr	*cdE/cde*	−	−	−	+	+	+	+	−	−	−
R^0r	*cDe/cde*	−	−	+	−	+	+	+	−	−	−
$R^{0v}r$	*cDeV/cde*	−	−	+	−	+	+	+	+	−	−
R^2r	*cDE/cde*	−	−	+	+	+	+	+	−	−	−
R^2R^2	*cDE/cDE*	−	−	+	+	+	−	−	−	−	−
$r'r$	*Cde/cde*	+	+	−	−	+	+	+	−	−	−
$r'r''$	*Cde/cdE*	+	+	−	+	+	+	−	−	−	−
$r'r^y$	*Cde/CdE*	+	+	−	+	−	+	−	−	−	−
R^1r^y	*CDe/CdE*	+	+	+	+	−	+	−	−	−	−
R^1r	*CDe/cde*	+	+	+	−	+	+	+	−	−	−
R^1R^0	*CDe/cDe*	+	+	+	−	+	+	+	−	−	−
$R^{1w}r$	C^wDe/cde	+	+	+	−	+	+	+	−	+	−
$R^{1x}r$	C^xDe/cde	+	+	+	−	+	+	+	−	−	+
R^1r'	*CDe/Cde*	+	+	+	−	−	+	−	−	−	−
R^1R^1	*CDe/CDe*	+	+	+	−	−	+	−	−	−	−
R^1R^2	*CDe/cDE*	+	+	+	+	+	+	−	−	−	−
R^1r''	*CDe/cdE*	+	+	+	+	+	+	−	−	−	−
$r'R^2$	*Cde/cDE*	+	+	+	+	+	+	−	−	−	−
R^1R^z	*CDe/CDE*	+	+	+	+	−	+	−	−	−	−
r^yr	*CdE/cde*	−	+	−	+	+	+	+	−	−	−
R^0r^y	*cDe/CdE*	−	+	+	+	+	+	+	−	−	−
R^2r	*CDE/cde*	−	+	+	+	+	+	+	−	−	−
R^zR^2	*CDE/cDE*	−	+	+	+	+	−	−	−	−	−
*Rh_zRh_z	*CCDEE	−	+	+	+	−	−	−	−	−	−
$\bar{R}\bar{R}$	*-D-/-D-*	−	−	+	−	−	−	−	−	−	−

* Phenotype: family not available.

TABLE 4. FAMILY ILLUSTRATING THE INHERITANCE OF THE $\mathbf{rh_i}$(Ce) BLOOD FACTOR THROUGH THE R^1 ALLELE

		Rh Antisera							
Individual	Blood Group	$\mathbf{Rh_0}$ D	rh″ E	hr′ c	hr f	rh′ C	hr″ e	$\mathbf{rh_i}$ Ce	Rh Genotype
I-1 Father	A	+	−	+	+	+	+	+	R^1r
I-2 Mother	O	+	+	+	+	+	+	−	R^0r^y
II-1 Brother	O	−	+	+	+	+	+	−	r^yr
II-2 Sister	O	+	−	+	+	−	+	−	R^0r
II-3 Sister	O	+	+	−	−	+	+	+	R^1r^y
II-4 Sister	O	+	−	+	+	−	+	−	R^0r
II-5 Sister	O	+	+	−	−	+	+	+	R^1r^y
II-6 Propositus	A	−	+	+	+	+	+	−	r^yr

Anti-$\mathbf{hr^v}$(V), anti-$\mathbf{rh^{w1}}$(C^w), and anti-$\mathbf{rh^x}$(C^x) used with negative results.

TABLE 5. EFFECT OF VARIATION OF Rh TYPE ON THE TITER OF ANTI-**rh$_i$**(Ce) AND OF SEVERAL ANTI-**rh′**(C) SERA

Test Serum	Technic	Test Cell and Titer						
		Rh$_1$Rh$_1$	Rh$_1$rh	Rh$_1^w$rh	Rh$_1^x$rh	rh′rh	Rh$_o$rh	rh$_y$rh
Anti-**rh$_i$**(Ce)	Ficin	32	16	12	8	16	0	0
Anti-**rh′**(C) #1	Ficin	128	128	32	4	128	2	2
Anti-**rh′**(C) #2	Saline	16	2	2	0	8	0	0
	Ficin	64	16	16	8	32	8	8
Anti-**rh′**(C) #3	Saline	8	4	4	2	4	4	3
	Ficin	32	32	32	16	32	32	12
Anti-**rh′**(C) #4	Saline	16	8	2	1	16	2	8
Anti-**rh′**(C) #5	Saline	*	*	*	*	32	*	16
	Ficin	*	*	*	*	256	*	192
Anti-**rh′**(C) #6	Ficin	*	*	*	*	1024	*	256

* Not tested because of the presence of anti-**Rh$_0$**(D).

Anti-**rh′**(C) sera: #1) "Pure" anti-**rh′**(C) from Rh$_2$Rh$_2$ donor kindly supplied by Dr. J. M. Staveley, New Zealand.

#2) "Pure" anti-**rh′**(C) from Rh$_2$rh donor kindly supplied by Dr. F. H. Allen, Jr., Boston.

#3) "Pure" anti-**rh′**(C) from rh donor, prepared by absorption of anti-**rh′** + anti-**Rh$_0$** with Rh$_2$ red cells.

#4) "Saline agglutinin" anti-**rh′**(C) plus blocked anti-**Rh$_0$**(D).

#5) Cross-reacting anti-**Rh$_0$′**(CD).

#6) Cross-reacting anti-**Rh$_0$′**(CD).

common variety of "saline agglutinin" anti-**rh′**(C) with blocked anti-Rh$_0$(D). The individual anti-**rh′**(C) sera yielded identical results although the reactions were not always of equal intensity. Three anti-**hr″**(e) sera were always in agreement. The results with anti-**rh$_i$**(Ce) reagent, however, differed from any previously described Rh specificity except that reported by Race *et al* (1954). Agglutination was found to occur only with test bloods containing Rh products derived from R^1 or r' alleles. The reactions of anti-**rh$_i$**(Ce) with various Rh types is summarized in table 3.

A family carrying R^1, r, R^0 and r^y alleles illustrates the dependence of **rh$_i$**(Ce) expression on the inheritance of R^1 rather than on the mere presence of the **rh′**(C) and **hr″**(e) factors in the test blood (table 4).

Variants of the **hr″**(e) factor were not encountered, but two variants of **rh′**(C) were available for tests. These were **rh^w**(C^w) as Rh$_1^w$rh (C^{w}cDee) and **rh^x**(C^x) as Rh$_1^x$rh (C^{x}cDee) (the latter kindly supplied by Dr. F. H. Allen, Jr., Boston, Mass.). Table 5 summarizes the reactions of anti-**rh$_i$**(Ce) with various Rh$_1$ and rh′ test cells, and shows that variants of the **rh′**(C) factor have an influence on the strength of reactions obtained with this reagent as well as with standard anti-**rh′** (C) sera.

The preceding data can be summarized by listing the products of various Rh alleles along with the serologic reactions that are theoretically expected of anti-**rh$_i$**(Ce) and other Rh antisera (table 6).

Race *et al* (1954) reported that certain anti-**C** sera gave negative reactions with *CdE/cde* and *CDE/cDe* red cells while certain anti-**E** sera gave weaker positive reactions with *Cde/cdE* and *CDe/cDE*. That is, *C* was suppressed in *CE/ce* (*cis configuration*) and *E* was weakened in *Ce/cE* (*trans configuration*). This was referred to as position effect following a practice established in experimental genetics (E. B. Lewis,

TABLE 6. THEORETICAL REACTIONS OF ANTI-**rh**$_i$(Ce) WITH THE PRODUCTS OF SOME Rh ALLELES

Gene Product	Rh Antisera									
	rh$_1$ Ce	**rh′** C	**Rh**$_0$ D	**rh″** E	**hr′** c	**hr″** e	**hr** f	**hr**^{v} V	**rh**^{w1} C^w	**rh**^{x} C^x
Rh$_1$ CDe	+	+	+	−	−	+	−	−	−	−
Rh$_1^w$ C^{w}De	+	+	+	−	−	+	−	−	+	−
Rh$_1^x$ C^{x}De	+	+	+	−	−	+	−	−	−	+
rh′ Cde	+	+	−	−	−	+	−	−	−	−
rh″ cdE	−	−	−	+	+	−	−	−	−	−
Rh$_2$ cDE	−	−	+	+	+	−	−	−	−	−
rh cde	−	−	−	−	+	+	+	−	−	−
rh^v cdeV	−	−	−	−	+	+	+	+	−	−
Rh$_0$ cDe	−	−	+	−	+	+	+	−	−	−
Rh$_0^v$ cDeV	−	−	+	−	+	+	+	+	−	−
rh$_y$ CdE	−	+	−	+	−	−	−	−	−	−
Rh$_z$ CDE	−	+	+	+	−	−	−	−	−	−
$\overline{\text{Rh}}$ -D-	−	−	+	−	−	−	−	−	−	−

1945) by which the phenotypic effect of closely linked loci, separable however, by recombination, depends on the combinations (cis or trans) in which they occur. In the case of the C−c and E−e blood factors, occupation of separate sites by *C*−*c* and *E*−*e* alleles has not been proved, nor can it be certain that separate *C*−*c* and *E*−*e* alleles in the different combinations (e.g., *cde*, *cDe*, *Cde*, *cdE*, *cDE*, *CdE*, *CDE*) are identical as required for proof of position effect.

The facts in the above case are that two antisera detected a factor derived only from R^1 and r'. Such antisera at least in the manner in which they were employed in this report, might thus be designated anti-**rh**$_i$(Ce). The case with weakening of **rh″**(E) reactions in certain combinations might be due to gene interraction at the phenotypic level analogous to the weakening of **Rh**$_0$(D) that is produced by an **Rh**$_0$(D) bearing allele when it is paired with r'(Ceppellini *et al*, 1955).

The anti-**rh′**(C) sera listed in table 5, despite the stronger reactivity of some for Rh$_1$ and rh′, failed to yield anti-**rh**$_i$(Ce) after absorption with either rh$_y$rh or Rh$_z$Rh$_2$ red cells. These sera, as well as several other anti-**rh′**(C) sera, behaved as though the anti-**rh′**(C) absorptive capacity of **rh′**(C)+ red cells was graded $r^y r \leq R^z r < R^1 r = r' r$. In the Ba serum, anti-**rh**$_i$(Ce) cross-reacting with **hr″**(e) and/or **hr**(f) may be isolated by absorption with **rh**$_i$−**hr″**+ (Ce−e+) red cells. On the other hand, available examples of what appeared to be anti-**rh**$_i$(Ce) cross-reacting with **rh′**(C) could not be isolated by absorption with **rh**$_i$ − **rh′** + (Ce−C+) blood.

The specificity of **rh**$_i$(Ce) is related to the problem posed by the Rh factor, **hr**(f). The blood factor **hr**(f) is a property of the products of ce bearing alleles, R^0 and r (Rosenfield *et al* 1953), and the blood factor **rh**$_i$(Ce) appears to be a property of the products of Ce bearing alleles, R^1 and r'.

From results of the bloods tested in this investigation, individuals found to have blood factor, **hr″**(e), also have either **hr**(ce) or **rh**$_i$(Ce). Reasoning within the Fisher-Race theory of separable Rh loci, both **hr**(ce) and **rh**$_i$(Ce) might be considered as variants of **hr″**(e) and thus alleles of E. Lack of demonstrable crossing over and recombination, however, is in support of a multiple allele theory for Rh (Wiener, 1943),

and from this it can be stated only that **hr**(ce) is shared by products of R^0 and r alleles, and that **rh**$_i$(Ce) is shared by products of R^1 and r' alleles. Future experience may disclose exceptions such as the product of r reported not to have **hr**(ce) (Sanger *et al* 1953); an allelic product having both **hr**(ce) and **rh**$_i$(Ce) remains a possibility. The **rh**$_i$(Ce) factor has not thus far extended the list of Rh alleles because, like **hr**(ce), it is produced by two established alleles.

DISCUSSION

An Rh blood factor, **rh**$_i$(Ce), a property of the products of established R^1 and r' alleles has been described. The antibody defining this factor was encountered in an Rh antiserum, Ba, that was considered to be anti-**rh**$'$(C) + **hr**$''$(e) until it was found not to react with Rh_zRh_z (CCDEE) and Rh_zRh_2 (CcDEE) test cells. After removal of anti-**hr**$''$(e) and/or anti-**hr**(f) by absorption with red cells of type rh (ccdee), Rh_0 (ccDee), Rh_2rh (ccDEe), rh_yrh (CcdEef), or Rh_zrh (CcDEef), the remaining antibody activity was found to differ from the specificity expected of anti-**rh**$'$(C) and to correspond to a specificity previously attributed to position effect (Race *et al* 1954).

Anti-**rh**$_i$(Ce) insofar as it is demonstrated in the Ba serum, might be questioned because of the loss of potency upon continued absorption with **rh**$_i$(Ce)− **hr**$''$(e)+ red cells. These results (see table 2) are reminiscent of unpublished experience (Rosenfield 1954) with the example of anti-**hr**(f) reported by Jones *et al* (1954). The native serum, Kr, a potent anti-**hr**$''$(e) could be absorbed with Rh_1Rh_1 (CCDee) red cells to leave a saline agglutinin with **hr**(f) specificity, but continued absorption especially with trypsin treated red cells removed all Rh antibody activity. The first example of anti-**hr**(f) was, in contrast, produced by an individual of type Rh_1Rh_2 (CcDEe), so that anti-**hr**(f) was the only Rh antibody present. It is presumed that eventually "pure" anti-**rh**$_i$ (Ce) will be produced by an individual of genotype R^zr, R^zR^0, or R^0r^y(CeDEef), and in the absence of known opportunity for cross-reaction within the Rh system, such a serum should withstand repeated absorption with any **rh**$_i$−(Ce−) blood.

The contrasting Rh factors, **rh**$'$-**hr**$'$(C−c) and **rh**$''$−**hr**$''$(E−e) have always attracted attention. The factors **hr**(f or ce) and **rh**$_i$(Ce) have been considered as variants of **hr**$''$(e) and thus serological properties that contrast with one another and also with **rh**$''$(E).

In the report of Sanger *et al* (1953), the specificity of an antiserum to detect F, a property contrasting to **hr**(f), was predicted to be similar to that of a mixture of anti-**rh**$'$(C) plus anti-**rh**$''$(E). Such an antiserum has not been encountered thus far. However, by similar reasoning, the specificity of an antiserum to detect **hr**$_i$(c or E), a property contrasting to **rh**$_i$(Ce), may be predicted, and an antibody with this specificity has been found. The isolated antibody was obtained in the eluate from type rh (ccdeef) red cells that were used for absorption of a serum containing anti-**rh**$''$(E) and anti-**hr**$'$(c) specificities (Rosenfield 1958). Since this antibody reacts with a property present in the products of all common Rh alleles except R^1 and r', it can be considered to react with **hr**$_i$(c or E), a property contrasting with **rh**$_i$(Ce). More such quasi-allelic relationships may be encountered before there is a better synthesis of the Rh locus.

The use of reagents such as anti-**hr**(f) and anti-**rh**$_i$(Ce) greatly increases the opportunity of identifying and "counting" Rh genes in population and genetic studies. These reagents also are of value in some cases of disputed paternity.

CONCLUSIONS

An Rh blood factor has been invoked to explain the reactions of an Rh antiserum with the products of established R^1 and r' alleles. This blood factor has been termed **rh**$_i$(Ce).

The Rh blood factor, **hr**(f or ce), has been considered as a property of the products of established R^0 and r alleles.

Anti-**rh**$_i$(Ce) appears to occur as a portion of the antibody activity of some anti-**rh**′(C) especially those obtained from Rh_2 donors. Absorption technic, however, fails to isolate anti-**rh**$_i$(Ce) from such anti-**rh**′(C) sera.

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BOOK REVIEW

Action of Radiation on Tissues: An Introduction to Radiotherapy

By A. LACASSAGNE AND G. GRICOUROFF. New York: Grune and Stratton, Inc., 1958, pp. 195, 17 photographs. $6.25.

THE TRANSLATION of Professors Lacassagne's and Gricouroff's little book by Dr. Lushbaugh and Miss Riese makes available a compact summary of much experimental ionizing radiation pathology that many of us in the United States would not know about because we do not read foreign languages well. Professor Lacassagne has been active in the fields of experimental and clinical radiobiology almost since their beginnings, and he includes many important observations made just before and after the turn of the century.

There is an introductory chapter, twelve chapters on the effects of radiation on organ systems, chiefly structural alterations, one on total body radiation, and a final one on effects of radiation on pathologic tissues. The ones on skin, male and female gonads, and hemopoietic tissues contain much useful material for they emphasize the immediate and late effects over a considerable dose range. The chapter on the respiratory tract is disappointingly short. The genetic aspects of radiation are treated seriously, but only briefly, in the chapter on effects on embryos. The accounts of what radiation does by its direct action to embryos and to the nervous system cover literature up to the early 1950's, but the intense work of more recent years is only briefly noted.

The action of radiation on tissues is an enormous subject and it is surprising how much of it has been compressed into this book. The authors have aimed it at young physicians preparing for practice, but this reviewer believes that radiobiologists and pathologists will also find it useful.

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RICHARD H. POST

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